ANNALS

OF

INTERNAL MEDICINE

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THE AMERICAN COLLEGE OF PHYSICIANS
VOLUME 55 • NUMBER 6

DECEMBER 1961

PROTECTION IN ITS SIMPLEST FORM

ESTOMUL™

IN ULCER THERAPY

ONE MEDICATION RELIEVES PAIN, INHIBITS EROSION, PROMOTES HEALING. UNIQUE IN SIMPLICITY, COMPLETENESS OF ACTION AND CONVENIENCE

Only ONE prescription to write

Riker

INDICATIONS:
Peptic Ulcer:
Duodenal Marginal
Gastric Esophageal
Hyperacidity and dyspepsia
Heartburn
Gastritis
Alcoholic gastritis
Gastroesophageal reflux
Esophagitis (without stricture)
Irritable bowel syndrome
Congenital shortening of esophagus
Chalasia of esophagus
Hiatus hernia of esophagus
Cardiospasm
Functional pylorospasm

DOSAGE:
Liquid and Tablets:
1 or 2 tablespoons or 1 or 2 tablets three times daily depending on severity of involvement.

SIDE ACTIONS:
Doses in excess of 6 tablets or 6 tablespoons daily may produce minor side actions such as dryness of the mouth or blurring of vision.

CONTRAINDICATIONS:
ESTOMUL should not be used in patients with organic pyloric obstruction or achalasia of esophagus. Use with caution in patients with renal impairment or insufficiency. Relative contraindications for anticholinergic drugs are glaucoma and prostatic hypertrophy which may lead to urinary bladder obstruction.

AVAILABILITY:
Tablets — Bottles of 100.
Liquid — Bottle of 12 fluid oz.

CAUTION: Federal law prohibits dispensing without prescription.

RESULTS	ACTIONS
	• ANTICHOLINERGIC orphenadrine hydrochloride
• RELIEVES SPASM AND REDUCES MOTILITY	ANTISPASMODIC
• RETARDS ACID PRODUCTION	ANTISECRETORY
• PROMPT REDUCTION OF PAIN	• TOPICAL ANESTHETIC orphenadrine hydrochloride
• RAPID AND PROLONGED NEUTRALIZATION OF GASTRIC HYDROCHLORIC ACID TO DESIRABLE pH LEVEL	• ANTACID aluminum hydroxide-magnesium carbonate co-precipitate
• COATS AND PROTECTS GASTRIC MUCOSA	• DEMULCENT bismuth aluminate
• INHIBITS EROSION OF MUCOSA	• ANTIPEPTIC bismuth aluminate

FORMULATION

Each ESTOMUL TABLET contains:		Each tablespoon (15 cc) ESTOMUL LIQUID contains:	
orphenadrine HCl [2-dimethylaminoethyl (2-methyl-benzhydryl) ether HCl]	25 mg.	orphenadrine HCl [2-dimethylaminoethyl (2-methyl-benzhydryl) ether HCl]	25 mg.
bismuth aluminate	25 mg.	bismuth aluminate	50 mg.
magnesium oxide	45 mg.		
aluminum hydroxide, magnesium carbonate co-precipitate	500 mg.	aluminum hydroxide, magnesium carbonate co-precipitate	918 mg.

RIKER LABORATORIES, INC., Northridge, California

Annals of Internal Medicine is published monthly at Prince and Lemon Streets, Lancaster, Pa. Subscription price per annum, net postpaid: $10.00, United States, Canada, Puerto Rico; $7.00 in the above countries, to bona fide medical students, interns, and residents; $12.00, other countries. Second-class postage paid at Lancaster, Pa.

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Fuller, H. L.: Angiology *11*:200 (June) 1960.

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Department of Surgery, University of Illinois College of Medicine, Chicago, Illinois

The authors of this new book have limited themselves for the past several years to intense study of the dissemination of cancer and its prevention. This monograph is the outgrowth of their research and findings. Every sentence has some definite bearing on the dissemination of cancer and its prevention.

The book details the lives of cancer cells, beginning with their detachment from the primary tumor, concentrating on the means of transportation by which they spread, and ending with the establishment by them of metastases. The authors stress particularly the unwitting role of the physician in the detachment of malignant cells. The mechanism of spread by vascular channels as well as the settling of cells in special localities and the subsequent production of secondary tumors, is also discussed at length.

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The chapters on Hyperthyroidism and Primary Aldosteronism in this revision have been almost entirely rewritten. The more recent developments with respect to genetic sex are stressed. Well documented case histories, taken serially when progression or response to treatment is pertinent, combined with life-like, exceptionally descriptive illustrations make you feel as though you are actually taking part in the bedside rounds as the authors report their clinical observations, laboratory reports, therapy and prognosis for each of the patients. Furthermore the authors present their specific recommendations as to case management rather than merely listing the possible therapeutic programs. A comprehensive, yet concise section entitled "Highlights of Hormone Therapy" now appears in the appendix.

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Plate 44: Fig. 1a Pronounced exophthalmos. Aged 67 years; had leg lesion 1 year before. Thyroid nodule present; no definite hyperthyroidism.

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1. Zarafonetis, Chris J. D.: Treatment of Scleroderma, Annals of Int. Med., 50:343-365 (1959)

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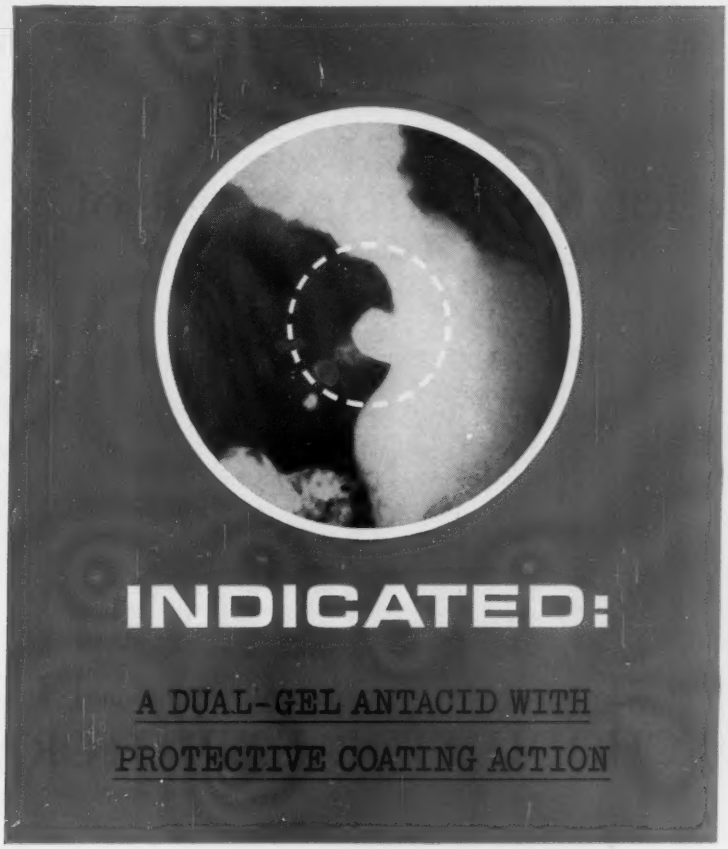

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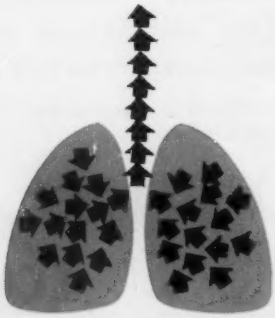
Glyceryl guaiacolate increases respiratory tract fluids which dilute the thick tenacious mucus in the bronchioles, facilitating its removal and thereby reducing obstruction.



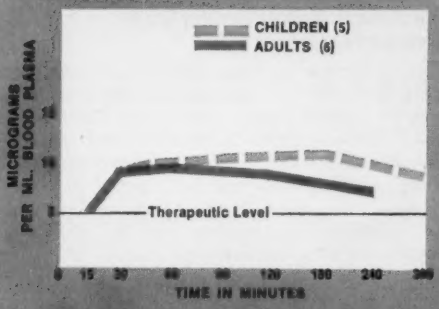
combines the bronchodilator effectiveness of theophylline[1-4]

with the proved expectorant action of glyceryl guaiacolate[5,6]

formulated for flexible low-volume dosage

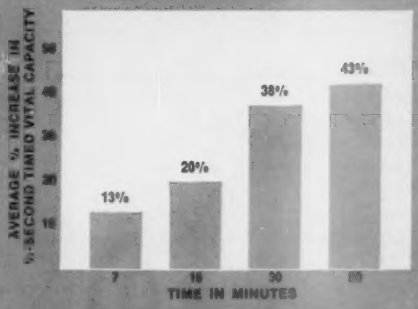
in a pleasant-tasting hydro-alcoholic vehicle for rapid absorption

QUIBRON RAPIDLY PROVIDES EFFECTIVE THEOPHYLLINE BLOOD LEVELS[7,8]



Following administration of Quibron elixir at the recommended dosage for adults[7] and children,[8] effective blood levels of theophylline were reached within 15–30 minutes and maintained for more than four hours.

THERAPY WITH QUIBRON IS FOLLOWED BY RAPID IMPROVEMENT OF VITAL CAPACITY[9]



Following administration of 20 ml. Quibron elixir, vital capacity was markedly improved, as measured by the timed ½-second method. Pulmonary function tests confirmed the clinical observation of rapid relief occurring in 10–15 minutes in most patients.[9]

Indications: Bronchial asthma, asthmatic bronchitis, chronic bronchitis and pulmonary emphysema.

Dosage & Administration: *Adults:* 1 to 2 tablespoons, 2–3 times daily. *Children, 6–12:* 1 tablespoon, 2–3 times daily. (Children weighing over 100 lbs. may require adult doses.) *Children under 6:* ½ teaspoon per 10 lbs. body weight, 2–3 times daily. During the first day of treatment, especially in severe attacks, the usual dose may be increased by one half.

Side Effects: Theophylline may cause gastric irritation, with possible abdominal discomfort, nausea and vomiting. The administration of Quibron elixir after meals may help avoid such symptoms. Theophylline may also exert some stimulating effect on the central nervous system.

Cautions: Quibron elixir should not be administered more frequently than every 6 hours or within 12 hours after rectal administration of any preparation containing theophylline or aminophylline. Other formulations containing xanthine derivatives should not be given concurrently with Quibron elixir.

Supplied: Each tablespoon of Quibron elixir (15 ml.) contains theophylline 150 mg. and glyceryl guaiacolate 90 mg. in a 15% hydro-alcoholic vehicle. Bottles of 8 fl. oz.

References: (1) Schluger, J.; McGinn, J. T., and Hennessy, D. J.: Am. J. M. Sc. *233*:296-302 (March) 1957. (2) MacLaren, W. R.: California Med. *91*:278-282 (Nov.) 1959. (3) MacLaren, W. R.: Ann. Allergy *17*:729-739 (Sept.-Oct.) 1959. (4) Spielman, A. D.: Ann. Allergy *15*:270-276 (May-June) 1957. (5) Cass, L. J., and Frederick, W. S.: Am. Pract. & Digest Treat. *2*:844-851 (Oct.) 1951. (6) Schwartz, E.; Levin, L.; Leibowitz, H., and McGinn, J. T.: Am. Pract. & Digest Treat. *7*:585-588 (April) 1956. (7) Schiller, I. W., and Goldman, G.: Personal communication on file at the Mead Johnson Research Center.* (8) Levin, S. J., and Weisnagel, J.: Personal communication on file at the Mead Johnson Research Center.* (9) Puls, R. J., and Grater, W. C.: Current Therap. Res., in press (Nov.) 1961.

*These data are available to physicians on request.

47161

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Symbol of service in medicine

No. 4 of a series reporting on Endo Laboratories' Anticoagulant Survey

Nationwide Survey Explores Current Use of Anticoagulants in Venous Thrombosis and Arterial Embolism

Immediate institution of anticoagulant therapy is now accepted by most physicians for the control of thrombotic disease affecting the veins. By inhibiting further propagation of an already formed thrombus, anticoagulation helps to reduce disability and prevent new and potentially fatal thromboembolic episodes.

These concepts of treatment are supported by the responses of 10,016 physicians who contributed their experience to Endo Laboratories' *Anticoagulant Survey* completed earlier this year. Analysis of the data showed that the use of anticoagulation was more often therapeutic than prophylactic.

Indication	All Anticoagulants	
	Therapeutically	Prophylactically
Acute Thrombophlebitis	69.9%	18.5%
Recurrent Chronic Thrombophlebitis	54.6%	30.4%
Deep Venous Thrombosis	69.5%	21.2%
Phlebothrombosis	53.7%	20.0%
Arterial Embolism	60.9%	22.5%
Pulmonary Embolism	66.7%	25.1%

Figures refer to percentage of physicians prescribing oral anticoagulants

Specialists Lead in Therapeutic Application of Anticoagulants

The chart below indicates the use of Coumadin—the most widely prescribed oral anticoagulant among both general practitioners and specialists—in the foregoing conditions. Proportionately, anticoagulation with this agent was employed to a greater extent by internists and cardiologists than by the responding general practitioners. For example, 76.9% of 2,626 specialists prescribing Coumadin most often used the drug therapeutically in *deep venous thrombosis* with its associated danger of pulmonary embolism, compared to 56.2% of 3,092 general practitioners using Coumadin.

Indication	General Practitioners	Specialists
Acute Thrombophlebitis	65.6%	82.5%
Recurrent Chronic Thrombophlebitis	48.7%	67.9%
Deep Venous Thrombosis	56.2%	76.9%
Phlebothrombosis	46.2%	66.9%
Arterial Embolism	53.2%	75.3%
Pulmonary Embolism	61.3%	84.2%

Figures refer to percentage of physicians prescribing Coumadin® therapeutically

Although anticoagulants were used less often for prophylaxis than for therapy, it is noteworthy that in *recurrent chronic thrombophlebitis*, for example, as high as 38.2% of the reporting specialists and 26.5% of the general practitioners employed Coumadin prophylactically.

Anticoagulants Minimize Mortality Due to Pulmonary Embolism

Through the use of anticoagulants in venous thrombosis, mortality from subsequent pulmonary emboli "can be reduced from 18 per cent to less than 1 per cent."[1] Anticoagulation is an established measure of choice in the management of thrombophlebitis.[1-3] Mead and Wright[1] suggest that ligation be reserved for those cases in which anticoagulation fails to stop the thrombophlebitic process, since the late effects of ligation are often undesirable.

Selection of Coumadin as the oral anticoagulant of choice offers the advantages of rapid, consistent effect and "predictability of dosage."[3] For routine postoperative protection against pulmonary embolism, Coumadin "appears to be the most predictable and consequently the safest and most effective anticoagulant drug..."[4] Since Coumadin, the first clinically established warfarin sodium, is presented in parenteral dosage forms for I.V. or I.M. administration as well as in a broad range of tablet potencies, it is the most versatile anticoagulant in hospital and office practice.

1. Mead, A. W., and Wright, I. S.: M. Clin. North America 45:907, 1961. 2. Olwin, J. H., and Koppel, J. L.: S. Clin. North America 39:193, 1959. 3. Kirtland, H. B., Jr., et al.: California Med. 92:409, 1960. 4. Belding, H. H.: West. J. Surg. 68:84, 1960.

Coumadin (warfarin sodium) is manufactured under license from the Wisconsin Alumni Research Foundation, and is supplied as scored tablets of 2 mg., lavender; 2½ mg., orange; 5 mg., peach; 7½ mg., yellow; 10 mg., white; and 25 mg., red, as well as in 50 mg. and 75 mg. single-injection units.

Another professional service of Endo Laboratories—makers of

COUMADIN®

the proven anticoagulant for long-term maintenance

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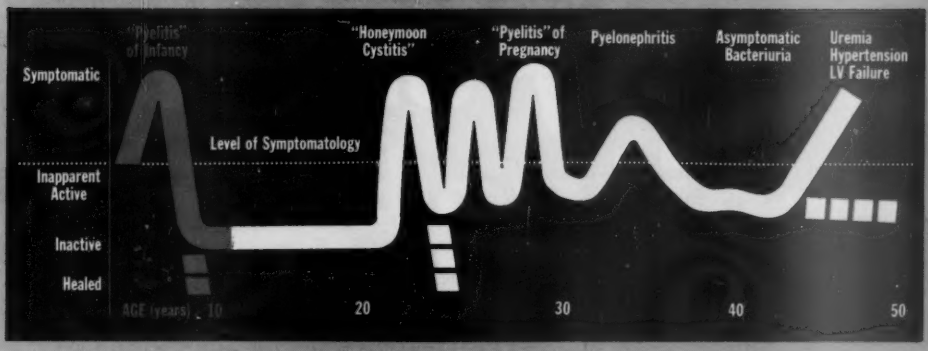
Natural History of Pyelonephritis



"... the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

in early childhood—"a potentially fatal warning sign"[2]

The *best* opportunity to eradicate urinary tract infection (and prevent potentially disastrous sequelae) is the *first* opportunity—in the infant and young child.

Furadantin—for a "cure" instead of a "chronic"

In children "a prophylactic regimen of therapy is indicated. . . . The therapy could be compared to the prophylactic treatment of patients whose exacerbation of a rheumatic fever has been controlled."[3] "Continuous prophylactic therapy with nitrofurantoin, at present, is our best modality for the treatment of chronic urinary tract infection."[4]

FURADANTIN DOSAGE FOR CHILDREN: Average dose is 5 to 8 mg. per Kg. (2.3 to 3.6 mg. per lb.) in 4 divided doses daily. A prophylactic dosage of from 1 to 5 mg. per Kg. is recommended for long-term use.[3] After the infection has been controlled, urinalysis and culture at least twice a year are suggested.[3]

SUPPLIED: Oral Suspension, 25 mg. per 5 cc. tsp., readily miscible with water, infant formulas, milk or fruit juices. Tablets, 50 mg. and 100 mg.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Stevenson, S. S.: J. Louisiana Med. Soc. *110*:219, 1958. 3. Marshall, M., Jr.: J. Kentucky Med. Assoc. *59*:35, 1961. 4. Johnson, S. H., III, and Marshall, M., Jr.: J. Urol. *82*:162, 1959.

Complete information in package insert or on request to the Medical Director.

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To cure or control infection throughout the urinary system at every age of life... at every stage of infection

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brand of nitrofurantoin

in any emetic situation

Tigan is safe and sound

Against nausea there's nothing more effective or, for that matter, quite so safe as Tigan. Tigan has only one demonstrable pharmacologic property: it blocks emetic impulses, primarily by direct action at the chemoreceptor trigger zone (CTZ) of the medulla. Tigan thus stops active vomiting as effectively as it prevents nausea. There are no special precautions, no known contraindications for Tigan therapy. Specifically an antiemetic, Tigan is not a converted antihistamine, tranquilizer or sedative—and may be used even where older antiemetics are contraindicated.

TIGAN 250-mg Capsules—so safe that it may be used with complete confidence as a routine "morning sickness" prescription in any pregnancy. Tigan 250-mg Capsules may also be prescribed with assurance in a wide range of other emetic situations where an antiemetic in oral dosage form is indicated.

TIGAN Injectable—in pre- and postoperative nausea and vomiting and in any emetic situation where it is desirable to have rapid onset of antiemetic action or when oral administration is not practical.

TIGAN Suppositories—especially indicated in pediatric practice. Offers full antiemetic potency, avoids the risk of extrapyramidal convulsive syndromes occasionally resulting from phenothiazine usage in children. Tigan Suppositories are particularly useful in children when oral administration is not feasible.

TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride

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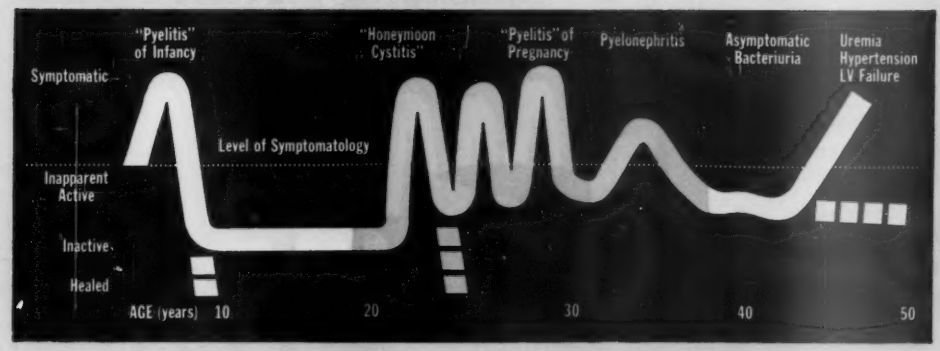
Natural History of Pyelonephritis



". . . the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

the child-bearing age—a second major stage for urinary tract infection

"The fact that the many cases of chronic and finally, lethal, upper urinary infections in women begin or recur during gestation is especially challenging."[2] "We now believe that all prepartum women should have one quantitative urine culture as part of their medical management."[3]

Furadantin—when pregnancy initiates (or activates) urinary tract infection

In a study of 104 pregnant women with urinary tract infections: "FURADANTIN was highly effective in the treatment of these infections during all stages . . . and frequently offers the best chance of effecting a clinical cure."[4]

FURADANTIN DOSAGE DURING PREGNANCY AND THE PUERPERIUM: The average dose is one 100 mg. tablet 4 times daily, given with meals and with food or milk on retiring, to prevent nausea. For acute, uncomplicated infections, 50 mg. q.i.d. may be administered. If improvement does not occur in 2 or 3 days, increase dosage to 100 mg. q.i.d.

SUPPLIED: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Benson, R. C., and Mitchell, J. C.: Clin. Obstet. Gynec. *1*:97, 1958. 3. Favour, C. B.: Southern Med. J. *54*:848, 1961. 4. Nesbitt, R. E. L., Jr., and Young, J. E.: Obstet. Gynec. (N. Y.) *10*:89, 1957.

Complete information in package insert or on request to the Medical Director.

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, NEW YORK

To cure or control infection throughout the urinary system at every age of life... at every stage of infection

Furadantin®

brand of nitrofurantoin

Where's the arthritic this morning?

Thanks to Medrol Medules, he woke up comfortable and he's already on the go.

The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

The slow, steady release of methylprednisolone often provides greater effectiveness, with less frequent administration and sometimes a reduced total daily dosage.

Many of your arthritic patients, too, can wake up comfortable on Medrol Medules.

Dosage: The following dosages are recommended in rheumatoid arthritis:

	Initial	*Maintenance*
Severe	12 to 16 mg.	6 to 12 mg.
Moderately severe	8 to 10 mg.	4 to 8 mg.
Moderate	6 to 8 mg.	2 to 6 mg.
Children	6 to 10 mg.	2 to 8 mg.

With Medrol Medules, it may be possible to reduce the total daily dose by ½.

Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications: Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief without developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Approximately 135 tiny "doses" mean smoother steroid therapy

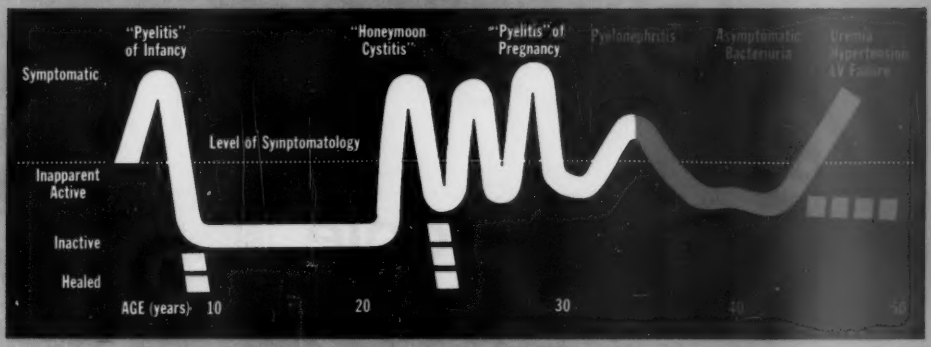
Each capsule contains: Medrol (methylprednisolone) 2 mg. or 4 mg. Supplied in bottles of 30 and 100.

Medrol* Medules*

Upjohn 75th year

*TRADEMARK, REG. U.S. PAT. OFF. COPYRIGHT 1961, THE UPJOHN COMPANY JUNE, 1961 THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Natural History of Pyelonephritis



"... the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

during the middle and later years—relapse, reinfection, renal failure

"... the physician treating a patient with established chronic urinary tract infection faces a grave problem of management."[2]

Furadantin—to preserve function; to prolong life

"... certain patients with renal insufficiency derived measurable benefit from prolonged nitrofurantoin treatment; as infection was suppressed their renal function improved. This effect was sufficiently pronounced to be considered an important component of the management of uremia accompanying chronic pyelonephritis."[2]

FURADANTIN DOSAGE IN LONG-TERM THERAPY: "With normal renal function, the dosage schedule of 50 mg. four times daily in adults gave urinary nitrofurantoin concentrations that usually exceeded 5 mg. per 100 mg. throughout the day. This level was thought to be sufficient, on the basis of bacterial sensitivity determinations."[3] In refractory cases, 100 mg. q.i.d. daily is recommended.

SUPPLIED: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Jawetz, E., et al.: A.M.A. Arch. Intern. Med. *100*:549, 1957. 3. Lippman, R. W., et al.: J. Urol. *80*:77, 1958.

Complete information in package insert or on request to the Medical Director.

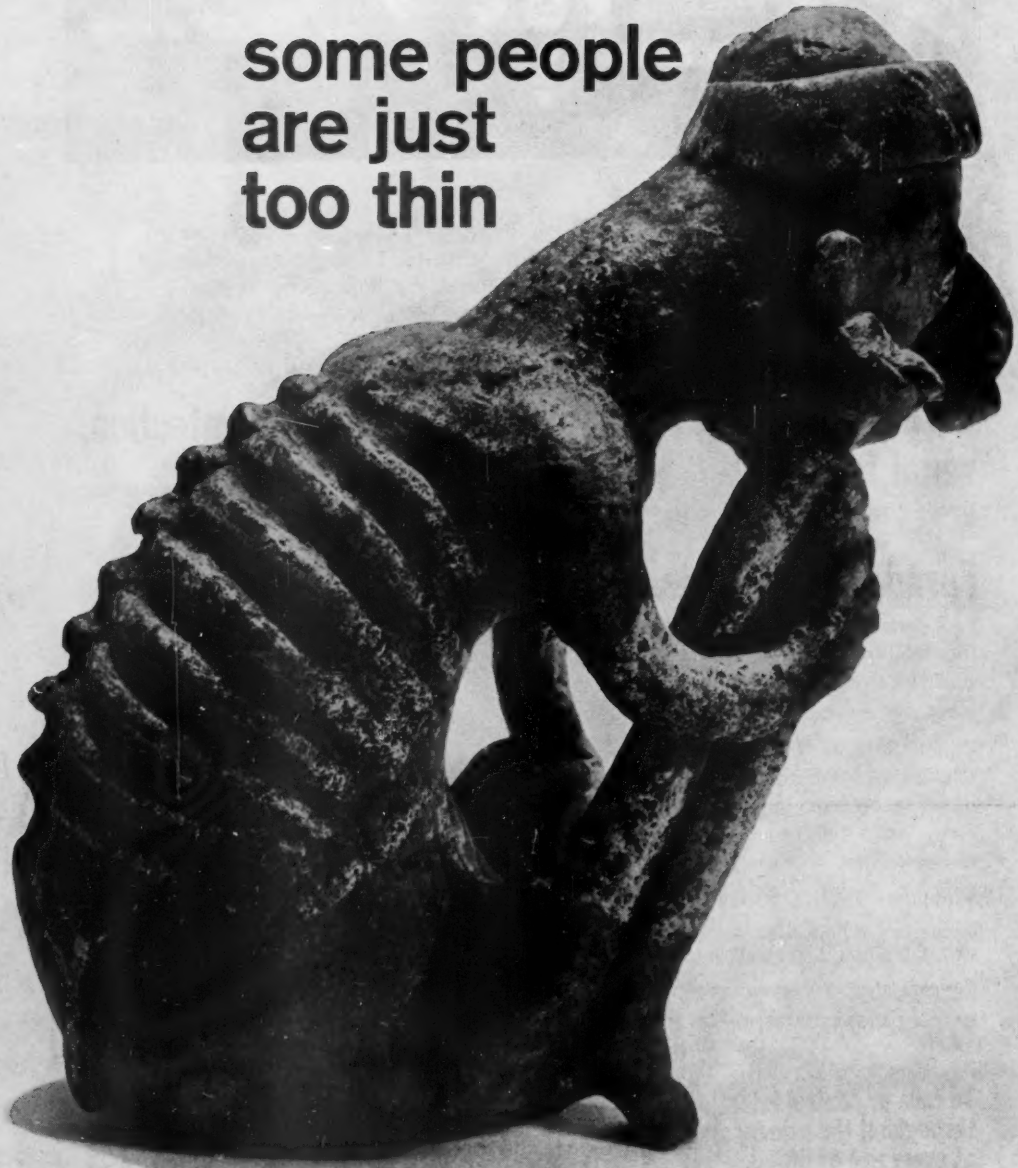
EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, NEW YORK

To cure or control infection throughout the urinary system at every age of life... at every stage of infection

Furadantin®

brand of nitrofurantoin

some people are just too thin



Effigies of pitifully emaciated people with ribs showing like "corrugated iron," such as this one from Nayarit, are typical of the tendency in primitive Western Mexican art to portray common illnesses and pathological deformations.

Dianabol® adds working weight

Most underweight, debilitated patients show both objective and subjective improvement after anabolic therapy with Dianabol. In the chronically underweight patient, as well as in patients wasted and weakened as a result of aging, chronic or acute illness, trauma, or surgery, Dianabol promotes lean weight gain (averaging 5½ pounds and often exceeding 10 pounds) within several weeks. What's more, by improving weight status and general physical condition, Dianabol renews vigor and revives a sense of well-being in the patient who is **too thin.**

Advantages of Dianabol over other anabolic agents:

■ **Dianabol has an unusually favorable anabolic/androgenic ratio.** The anabolic effects of Dianabol occur at dosages which generally preclude androgenic side reactions. In this respect, Dianabol proved superior to 12 other anabolic agents.*

■ **Dianabol is economical.** Low in cost, Dianabol is especially suitable for the chronically ill patient who may require long-term therapy.

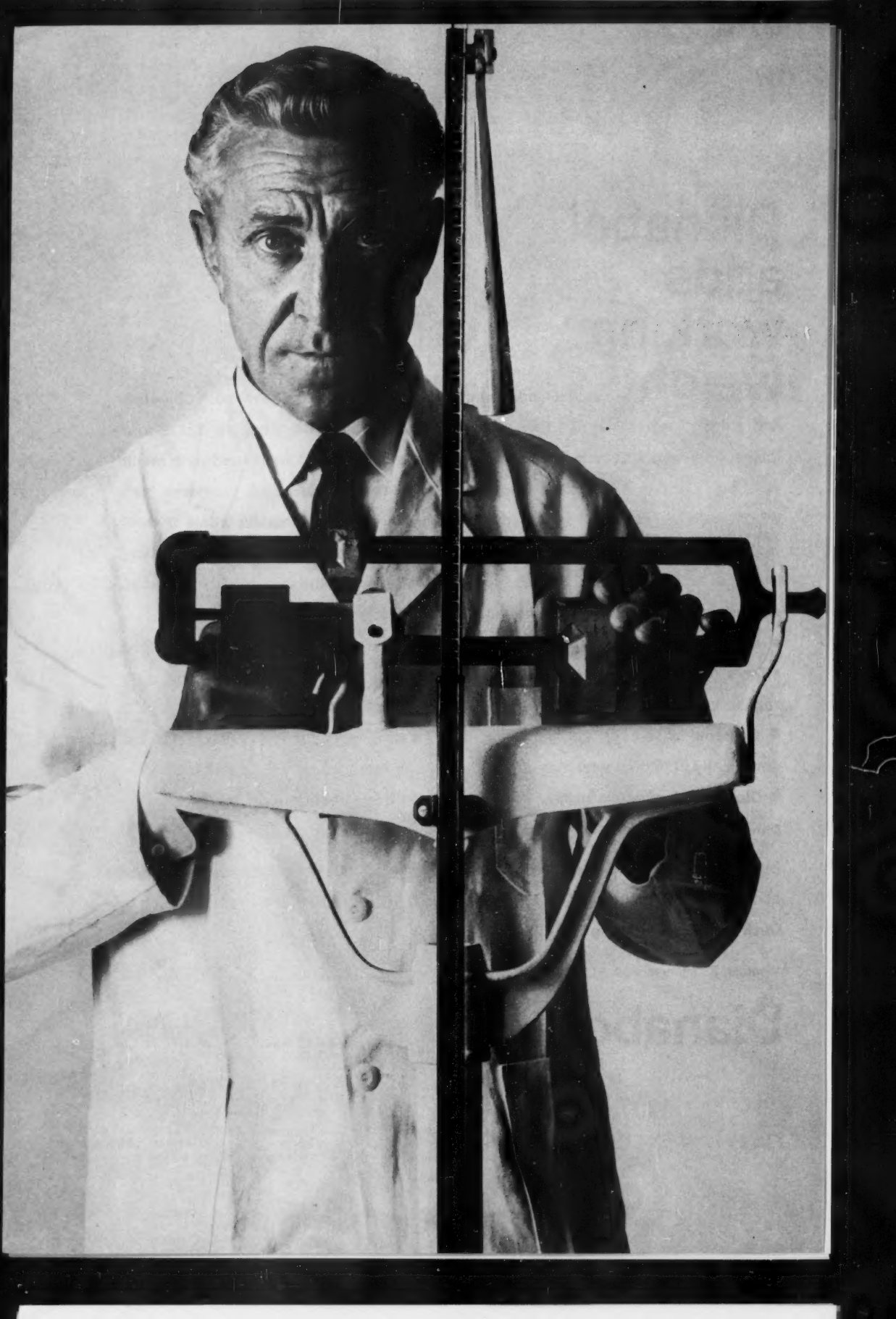
■ **Dianabol is effective orally.** Because it is an oral preparation, Dianabol spares patients the inconvenience and discomfort of parenteral drugs.

SUPPLIED: **Tablets,** 5 mg. (pink, scored); bottles of 100. For complete information about Dianabol (including dosage, cautions, and side effects), see current Physicians' Desk Reference or write CIBA, Summit, N. J.

*Misurale, F.: Minerva med. 51:996 (March 21) 1960.

Dianabol® (methandrostenolone CIBA) z/2986MD

CIBA
Summit, N. J.



Can we measure the patient's comfort?

The physician can measure body weight by means of a scale. But he has no instrument—no objective test—for measuring comfort.

For this, he must depend upon his own powers of observation and the patient's own description of how he feels.

Because these are, admittedly, subjective criteria, the validity of results hinges entirely on the experience and objectivity of the investigators involved.

Such well-qualified clinicians have reported that a new corticosteroid developed in the research laboratories of Upjohn actually raises the level of relief obtainable with this type of therapy.

This difference cannot be "proved." It must be seen. And the only practical way for you to do this is to evaluate this new drug critically in your own practice. Please do, at your first opportunity. We are confident that you will be glad you did.

The new corticosteroid from Upjohn research

Alphadrol*

Each tablet contains Alphadrol (fluprednisolone) 0.75 mg. or 1.5 mg.
Supplied in bottles of 25 and 100.

The anti-inflammatory activity of Alphadrol is comparable to the best effects obtained in current practice. Results obtained with Alphadrol have been such as to warrant classifying it among the most efficient steroids now available.

More than twice as potent as prednisolone, Alphadrol exhibits no new or bizarre side effects. Salt retention, edema or hypertension, potassium loss, anorexia, muscle weakness or muscle wasting, excessive appetite, abdominal cramping, or increased abdominal girth have not been a problem.

Indications and effects
The benefits of Alphadrol (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) are indicated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications
Patients on Alphadrol will usually experience dramatic relief *without* developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne or emotional imbalance.

As in all corticotherapy, however, there are certain precautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Alphadrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

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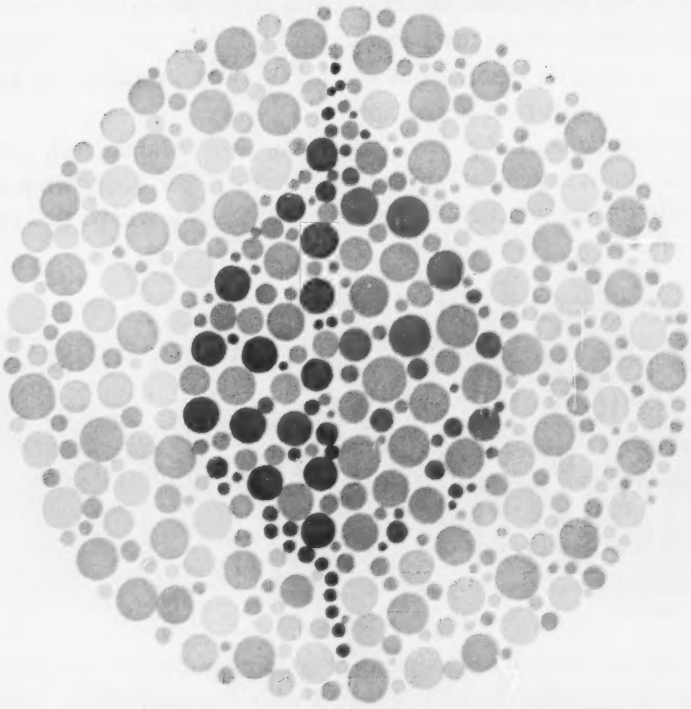
August, 1961

The Upjohn Company, Kalamazoo, Michigan **Upjohn**

"SEEING YELLOW" ON DIGITALIS LEAF 61-year old male with syphilitic heart disease, cardiac enlargement Grade II, sinus rhythm, right bundle block and aortic insufficiency. Evaluated to be in class III-C. For 11 months, he took 0.1 Gm. of digitalis leaf daily. Admitted to hospital because of nausea, vomiting and disturbance in color-vision. Medication was discontinued for 30 days, after which he was redigitalized with digitoxin and discharged on 0.1 Gm. digitalis leaf daily. Four days later he was readmitted with nausea, vomiting, disturbed color-vision. Digitalis again discontinued for 5 days and toxic symptoms disappeared. Patient then placed on GITALIGIN, 0.5 mg. per day. There were no toxic signs or symptoms and failure was well controlled.[1]

"DIGITALIS TOXICITY IS SEEN WITH INCREASING FREQUENCY TODAY..."[2]



for maximal digitalis activity with minimal toxicity

Gitaligin®†

"...patients who became toxic very readily with other agents could later be satisfactorily digitalized with gitalin (GITALIGIN)."[2]
Wider margin of safety—frequently effective in patients refractory to other digitalis glycosides • broader clinical utility—therapeutic dose only ⅓ the toxic dose • faster rate of elimination than digitoxin or digitalis leaf. □ Supplied: 0.5 mg. scored tablets—bottles of 30 and 100.

1. Dimitroff, S. P. et al.: Ann. Int. Med. 39:1189, 1953. 2. Pastor, B. H.: GP 22:85, 1960.

†amorphous gitalin, White

WHITE LABORATORIES, INC. • Kenilworth, New Jersey

Metamine®
(trolnitrate phosphate, Leeming, 10 mg.)
Sustained

in coronary insufficiency

helps you dilate the coronaries

In pharmacologic studies at Pasteur Institute and McGill University, the vasodilator activity of trolnitrate phosphate (METAMINE) was found to be equal or superior to that of nitroglycerin, and of much longer duration.[1-2]

In coronary insufficiency, one METAMINE SUSTAINED tablet q. 12 h. markedly reduces the number and severity of anginal attacks and increases exercise tolerance, with virtual freedom from nitrate side effects and less danger of a forgotten dose.[3-4] Bottles of 50 and 500 tablets.

Thos. Leeming & Co. Inc.

New York 17, N. Y.

1. Bovet, D., and Nitti-Bovet, F.: Arch. internat. de pharmacodyn. et therap. 83:367, 1946. 2. Melville, K.I., and Lu, F.C.: Canad. M.A.J. 65:11, 1951. 3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956. 4. Eisfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

1 tablet all day

1 tablet all night

Theragran®

SQUIBB VITAMINS FOR THERAPY

For your patients with infections or other illnesses who need therapeutic vitamin support. Each Theragran supplies the essential vitamins in truly therapeutic amounts:

Vitamin A	25,000 U.S.P. Units
Vitamin D	1,000 U.S.P. Units
Thiamine Mononitrate	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Vitamin C	200 mg.
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	20 mg.
Vitamin B_{12}	5 mcg.

SQUIBB *Squibb Quality—the Priceless Ingredient*

'Theragran'® is a Squibb trademark

"nutrition...present as a modifying or complicating factor in nearly every illness or disease state"[1]

1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958

cardiac diseases "Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2] 2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

arthritis "It is our practice to prescribe a multiple vitamin preparation to patients with rheumatoid arthritis simply to insure nutritional adequacy . . ."[3]
3. Fernandez-Herlihy, L.: Lahey Clinic Bull. 11:12 (July-Sept.) 1958.

digestive diseases Symptoms attributable to B-vitamin deficiency are commonly observed in patients on peptic ulcer diets.[4] Daily administration of therapeutic vitamins to patients with hepatitis and cirrhosis is recommended by the National Research Council.[5] 4. Sebrell, W. H.: Am. J. Med. 25:673 (Nov.) 1958. 5. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 57.

degenerative diseases "Studies by Wexberg, Jolliffe and others have indicated that many of the symptoms attributed in the past to senility or to cerebral arteriosclerosis seem to respond with remarkable speed to the administration of vitamins, particularly niacin and ascorbic acid. These facts indicate that the vitamin reserve of aging persons is lowered, even to the danger point, more than is the case in the average American adult."[6] 6. Overholser, W., and Fong, T.C.C. In Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 264.

infectious diseases Infections cause a lowering of ascorbic acid levels in the plasma; and the absorption of this vitamin is reduced in diarrheal states.[7] 7. Goldsmith, G. A.: Conference on Vitamin C. The New York Academy of Sciences, New York City, Oct. 7 and 8, 1960. Reported in: Medical Science 8:772 (Dec.10) 1960.

diabetes Diabetics, like all patients on restricted diets, require an extra source of vitamins.[8] "Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet. . . . There is some evidence of interference with normal riboflavin utilization during catabolic episodes."[9]
8. Duncan, G. G.: Diseases of Metabolism 4th edition W. B. Saunders, Philadelphia, 1959, p. 812. 9. Pollack, H.: Am. J. Med. 25:708 (Nov.) 1958.

FOR FULL INFORMATION SEE YOUR SQUIBB PRODUCT REFERENCE OR PRODUCT BRIEF.

IN FUNCTIONAL G.I. AND BILIARY DISTURBANCES ...TO EACH PATIENT ACCORDING TO THE NEED

DECHOLIN-BB®

Hydrocholeretic • Antispasmodic • Sedative...to reduce *TENSION* and anxiety-induced dysfunction of G.I. and biliary tracts...and also relieve both smooth-muscle *spasm* and biliary/intestinal *stasis*

butabarbital sodium ..... 15 mg. (¼ gr.)
(Warning–may be habit forming)
dehydrocholic acid, AMES .....250 mg. (3¾ gr.)
belladonna extract ..... 10 mg. (⅙ gr.)

DECHOLIN® with Belladonna

Hydrocholeretic–Antispasmodic...to relax *SPASM* of smooth muscle of G.I. tract and sphincter of Oddi...and also counteract biliary/intestinal *stasis*

dehydrocholic acid, AMES .....250 mg. (3¾ gr.)
belladonna extract ..... 10 mg. (⅙ gr.)

DECHOLIN®

Hydrocholeretic...to combat *STASIS* in bowel and biliary tract...by activating biliary function with a greatly increased flow of aqueous "therapeutic" bile

dehydrocholic acid, AMES .....250 mg. (3¾ gr.)

Average adult dose: 1 or, if necessary, 2 tablets three times daily.

Side effects: DECHOLIN by itself, or as an ingredient, may cause transitory diarrhea. Belladonna in DECHOLIN with Belladonna and DECHOLIN-BB may cause blurred vision and dryness of mouth.

Contraindications: Biliary tract obstruction, acute hepatitis, and (for DECHOLIN with Belladonna and DECHOLIN-BB) glaucoma.

Precautions: Periodically check patients on DECHOLIN with Belladonna and DECHOLIN-BB for increased intraocular pressure. Also observe patients on DECHOLIN-BB for evidence of barbiturate habituation or addiction, and warn drivers against any risk of drowsiness.

Available: DECHOLIN-BB, in bottles of 100 tablets; DECHOLIN with Belladonna and DECHOLIN, in bottles of 100 and 500.

11161

AMES
COMPANY, INC
Elkhart • Indiana
Toronto • Canada

NEW PRODUCT

End the Spin and Spell of "Dizziness"

vertigo • nausea • vomiting

impaired cerebral circulation

labyrinthine dysfunction

related conditions

● **TWO SPECIFIC ACTIONS** ● **FEWER SIDE REACTIONS** New Tigacol facilitates the symptomatic control of vertigo. It relieves the varied symptoms of vertigo whether due to labyrinthitis, Meniere's syndrome, impaired cerebral circulation or of nonspecific origin. Tigacol offers you the clinically proven advantages of a well-tolerated peripheral vasodilator and a new specific antiemetic. **Roniacol** promptly relieves vertigo by directly relaxing the peripheral blood vessels without causing severe flushing or hypotension. **Tigan** controls nausea and vomiting by selective suppression of emetic impulses without drowsiness, tranquilization or adrenergic effects.

AVAILABLE: Pink capsules, each providing 50 mg Roniacol in the form of the tartrate and 100 mg Tigan HCl, bottles of 50. **USUAL ADULT DOSAGE:** One or two capsules three times daily. **NOTE:** Side effects were virtually absent except for a few instances of flushing and an occasional case of skin rash, which disappeared when medication was withdrawn. There are no known contraindications, but as with any new drug, patients should be observed periodically while on Tigacol therapy.

RONIACOL® — brand of nicotinyl alcohol • TIGAN® — 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl)benzylamine

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

TIGACOL

when the complaint is "dizziness"

new treatment "puts water to work" to relieve dry...itchy skin associated with internal disorders

Buffalo, N. Y. The discomforts of dry, itchy skin associated with internal disorders can now be relieved by Alpha-Keri, a new treatment that actually "puts water to work." This is important because effective moisturizing of skin provides immediate symptomatic relief for most dryness and itching.

Several years were spent in developing Alpha-Keri. This new product is the first and only completely water-dispersible, antipruritic oil combining mineral oil and a skin moisturizer.* When added to bath water, Alpha-Keri turns milky white because this unique oil is emulsified immediately into microfine particles which are deposited over the entire skin area.

These microfine oil particles cling to the skin, forming a fine, invisible film that not only supplies needed moisture, but actually "locks moisture in" by retarding evaporation. This film also lubricates and protects the skin by replacing the action of natural oils lost by the drying out effects of soap, water and weather. And, Alpha-Keri soothes the skin to relieve itching.

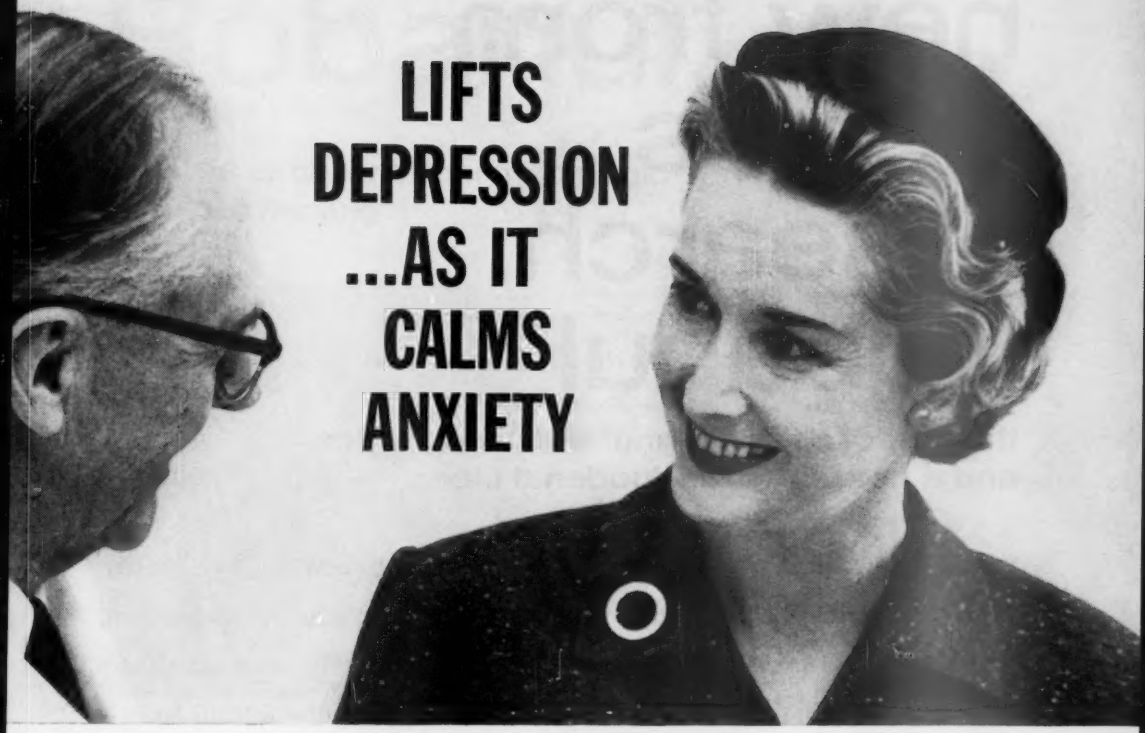
Alpha-Keri relieves the discomforts of dry, itchy skin in a wide variety of conditions including winter-itch; bath-itch; pruritus senilis; chafed or chapped skin; ichthyosis; neurodermatitis; soap dermatitis, and contact dermatitis.

Alpha-Keri is always used with water ... added to water or rubbed into wet skin. Alpha-Keri may be added to the bath or sponged on the wet skin while showering. It is also an excellent emollient cleanser for dry hands. Available in 8 oz. bottles.

*Kerohydric® (brand of dewaxed, oil-soluble, keratin-moisturizing fraction of lanolin).

Write for samples and literature.

WESTWOOD
PHARMACEUTICALS
BUFFALO 13, NEW YORK



"I feel like my old self again!" Thanks to your balanced Deprol therapy, normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly – you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver damage, hypotension or tachycardia.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be increased gradually up to 3 tablets q.i.d. With establishment of relief, the dose may be reduced gradually to maintenance levels.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

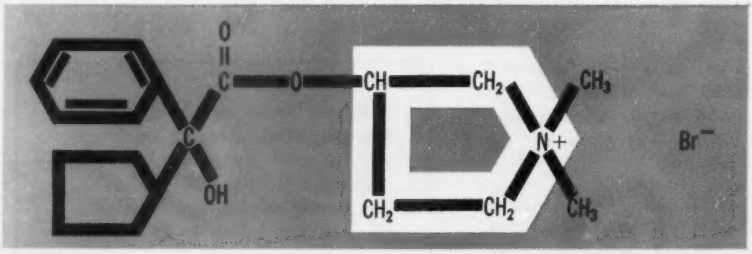
WALLACE LABORATORIES / *Cranbury, N. J.*

cp-5858

new from Robins research: Robanul™

the first of the rigid-ring* anticholinergics and a new drug for duodenal ulcer

With the recent introduction of **Robanul,** the A. H. Robins Co. now gives the physician an important new synthetic anticholinergic. An original Robins development, **Robanul** and its companion product **Robanul-PH** (for phenobarbital) have shown that they can produce within 90 minutes—and maintain for 6 to 10 hours—conditions conducive to prompt relief of ulcer pain and successful recovery for your ulcer patient.



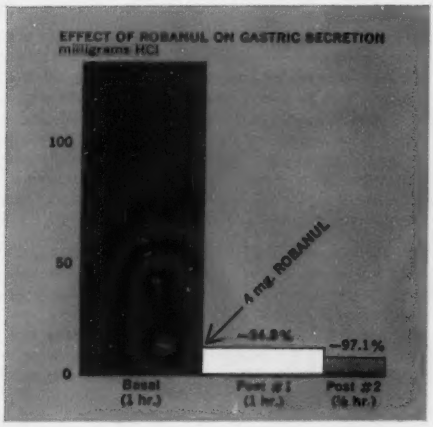
Robanul represents a unique chemotherapeutic application of the "rigid-ring" concept. Its active molecular elements are built onto a five-membered ring that cannot vary appreciably in shape or pattern. Thus, the reactive sites of the Robanul molecule are "locked" at fixed atomic distances. It is this spatial rigidity that biochemists theorize is responsible for Robanul's predominantly gastrointestinal specificity, its potency, and particularly its low incidence of typical anticholinergic side effects.[1]

*Used to describe the fixed atomic distances between reactive sites within the Robanul molecule.

Robanul™ (pronounced ró-ban-ul)

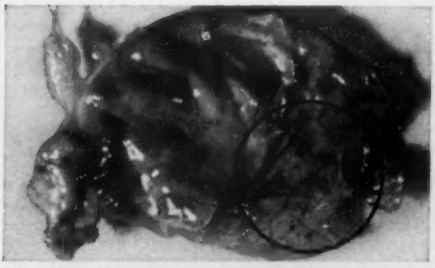
glycopyrrolate,** Robins

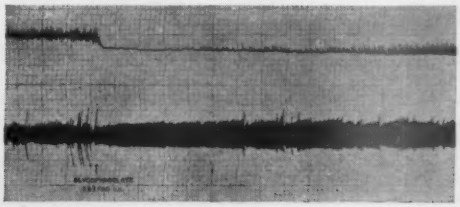
creates excellent pharmacologic conditions for ulcer healing

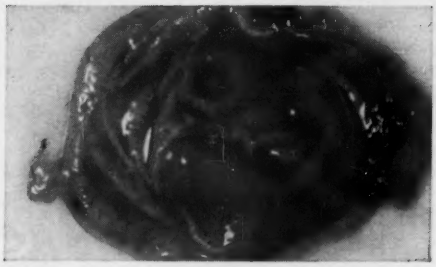


In studies of acid inhibition,[2] proponents of the "no acid —no ulcer" school will be pleased to note that a 4 mg. dose of Robanul reduced the acidity of gastric secretions 94.4% within one hour! Volume dropped as well, falling off 30% within 30 minutes, and another 30% in the next 15 minutes.

In suppressing g.i. spasm, Robanul showed marked vigor and evidence of selectivity. This antihypermotility tracing from a dog shows definite lowering of intestinal tone after Robanul. Bottom line is respiration. In humans, one study[3] showed that within 40 minutes after a 2 mg. dose, gastric antral contractions decreased from 2½ per minute to 0.4 per minute.







Anti-ulcer effect of Robanul is seen in the Shay rat procedure which creates an ulcerogenic situation artificially by ligating the pylorus and allowing the stomach contents to collect. Note the multiple lesions in the stomach of the untreated control animal (top) as compared to ulcer-free stomach from the rat treated with Robanul (bottom).[4]

SUMMARY OF BASIC BROCHURE: OVER

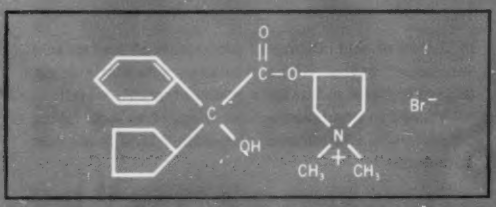
**U.S. patent number 2,956,062

Robanul™

glycopyrrolate, 1.0 mg. per tablet

Robanul™-PH

glycopyrrolate, 1.0 mg., with phenobarbital, 16.2 mg., per tablet



description: Robanul is a new anticholinergic agent which helps provide the conditions of reduced gastric acidity and motility that add up to a more favorable ulcer-healing environment. Chemically, it is 1-methyl-3-pyrrolidyl α-phenylcyclopentaneglycolate methobromide. Robanul exerts a more specific pharmacologic action on the g.i. tract than on any other organ system. Thus, the common extensions of anticholinergic action (dry mouth, blurred vision) occur only rarely at Robanul's optimum dosage range.

In peptic ulcer (gastric or duodenal) a positive therapeutic response was seen in 92% of patients. Many reported relief of symptoms within 24 hours. The duration of action was 6-10 hours, assuring overnight control of symptoms. Robanul has also shown outstanding effectiveness in other g.i. complaints.

Of 1,009 patients, 923 (over 91%) improved following Robanul or Robanul-PH therapy. Where indicated, Robanul-PH was used (272 cases) with over 80% receiving prompt and prolonged relief of symptoms.[5]

pharmacology: In animals, Robanul showed marked anticholinergic effects. It inhibited histamine and insulin induced gastric secretions, with particular effect on the latter. More important, it completely inhibited the gastric response to large quantities of food at doses well below the toxic level.[4]

indications: In addition to its primary indication in duodenal and gastric ulcer, Robanul is indicated for conditions that are helped by a decreased concentration and volume of stomach acid; for g.i. disorders associated with hypermotility; and in other conditions for which anticholinergic action may be desirable, for example: duodenitis, pylorospasm, gastritis, hyperchlorhydria, and pyrosis. Also for functional gastroenteritis, cardiospasm, spastic and irritable colon, functional bowel distress, functional diarrhea, and neurogenic gastrointestinal disturbances.

Robanul-PH is indicated when mild anxiety or tension is present in these conditions.

dosage: On an average: one tablet (1 mg.) t.i.d. (morning, early afternoon, and at bedtime) for both Robanul and Robanul-PH. Some patients may require an extra tablet at bedtime to assure overnight control of symptoms. For maintenance: one tablet b.i.d. will frequently control symptoms adequately. In acute conditions with severe manifestations, larger doses (two Robanul tablets, t.i.d.) may be used until symptoms subside. Thereafter, dosage should be reduced to the minimum required to attain symptomatic relief.

side effects: At the recommended dose of Robanul (1 to 4 mg. daily), one encounters few side effects, such as dry mouth, blurred vision, constipation, and urinary retention, usually associated with anticholinergic drugs. At this dosage level, only 22 of 499 patients (4.4%) had complaints of side effects of a moderate to severe degree. Constipation was slightly more frequent with Robanul-PH.

The most frequently encountered of the side effects noted in all preliminary studies was dry mouth. Yet only thirty-three (3.3%) of 1,009 patients who received 1 to 32 mg. of Robanul or Robanul-PH daily, complained of dry mouth, and only eleven of these discontinued the medication because of this reaction. Eleven more discontinued treatment because of the following complaints: rash (3 patients); urinary difficulties (2); nausea (2); bitter taste, nervousness, constipation, and abdominal cramps (one patient in each category). Significant blurred vision was noted in only 5 patients.

precautions and contraindications: Robanul is contraindicated in conditions involving obstruction of the urinary bladder neck, pyloric obstruction, and gastric or duodenal ulcer causing stenosis and significant gastric retention.

Sensitivity to phenobarbital contraindicates the use of Robanul-PH. Though an exacerbation of glaucoma has not been noted with Robanul, it should be used with care in patients with known or suspected glaucoma.

supply: Robanul: scored, compressed, pink tablets, containing 1.0 mg. of glycopyrrolate, bottles of 100 and 500. Robanul-PH: scored, compressed, blue tablets, containing 1.0 mg. of glycopyrrolate and 16.2 mg. of phenobarbital, bottles of 100 and 500.

references: 1. Franko, B.V., and Lunsford, C. D.: Derivatives of 3-Pyrrolidinols-III. The Chemistry, Pharmacology, and Toxicology of some N-substituted-3-Pyrrolidyl α-Substituted Phenylacetates, J. Med. Pharmaceut. Chem. 2:523, 1960. 2. Moeller, H. C.: Physiological Effect and Clinical Evaluation of Glycopyrrolate in Peptic Ulcer Disease, presented at the N.Y. Acad. of Sc., Oct., 1961. 3. Breidenbach, W. C., investigative clinical report, March, 1961. 4. Ward, J. W., et al.: Pharmacodynamic Evaluation of Glycopyrrolate in Animals, presented at the N.Y. Acad. Sc., Oct., 1961. 5. Clinical reports from 42 investigators on file in the Medical Department of the A. H. Robins Co., Inc., Mar., 1961.

bibliography: Abbott, W. E., Kriegler, H., and Sourial, A.: "Physiological and Clinical Evaluation of Gastric Acidity with Glycopyrrolate, Histamine and Insulin Stimulation," presented at N.Y. Acad. Sc., Oct., 1961. Epstein, J. H.: "Clinical Observations with a New Anticholinergic, Glycopyrrolate," Am. J. of Gastroenterol. (in press). Ruffin, J., and Cayer, D.: "The Role of Anticholinergic Drugs in the Treatment of Peptic Ulcer Disease," presented at the N.Y. Acad. Sc., Oct., 1961. Sun, David, C. H.: "Comparative Pharmacological and Physiological Effects of Glycopyrrolate and Propantheline," ibid. Young, R.: "Action of Glycopyrrolate on Gastrointestinal Motility," ibid.

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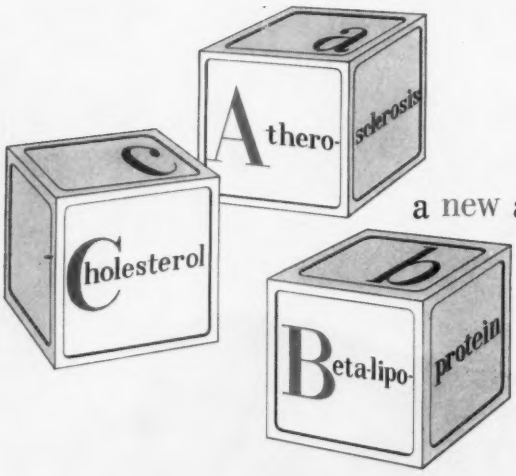

a new approach to these A-B-C's

A recent review of the **atherosclerosis** problem[1] points out that "**cholesterol** is only one of the serum lipids which may be related in some way to atherogenesis" and suggests that "specific triglycerides, phospholipids, fatty acids or the whole spectrum of **beta-lipoproteins** may be of equal or greater importance."

The role of the low-density beta-lipoproteins has been stressed by Olson[2], who suggests that they are the primary agents in atherosclerosis. Another recent discussion[3] has brought out the need for a simple and reliable testing procedure for beta-lipoproteins.

BETA-L TEST® is a specific immunochemical test for estimating serum beta-lipoprotein levels. BETA-L TEST reagent contains antibodies which specifically precipitate the beta-lipoproteins in human sera. This precipitate is then measured visually. Test requires only one drop of patient's serum and can be performed in 10 minutes. Clinical laboratories equipped with a micro-hematocrit centrifuge need no other special equipment for test performance.

In addition to its usefulness in atherosclerotic studies, BETA-L TEST may be found a helpful diagnostic and prognostic procedure in diabetes, hypothyroidism, the menopausal state and other conditions associated with elevated beta-lipoproteins.

BETA-L TEST measurements correlate well with total beta (low-density) lipoprotein measurements obtained by electrophoresis[4] and polyanion precipitation[4] and with cholesterol values in the beta-lipoproteins[5].

BETA-L TEST is supplied in 60-test kits.

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4. Heiskell, C. L., et al.: A Simple Method for Quantitation of Serum Beta-Lipoproteins by Means of the Immunocrit, Amer. J. Clin. Path. *35:* 222-226 (March) 1961.

5. Bergquist, L. M., Carroll, V. P., Jr., and Searcy, R. L.: Evaluation of a Specific Antiserum for Serum-β-Lipoprotein Estimations, Lancet *i:* 537-538 (March 11) 1961.

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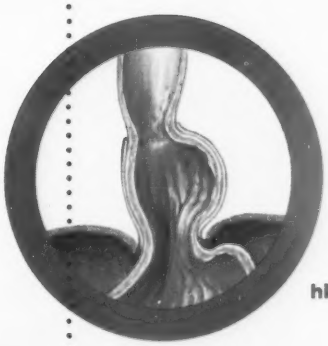
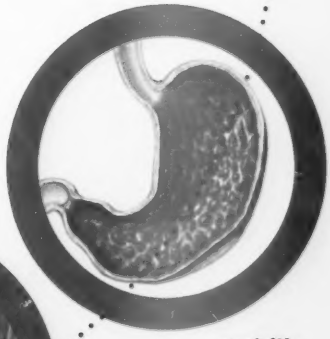
In gastric disorders: physician-preferred agents to relieve symptoms and promote recovery

Wyeth

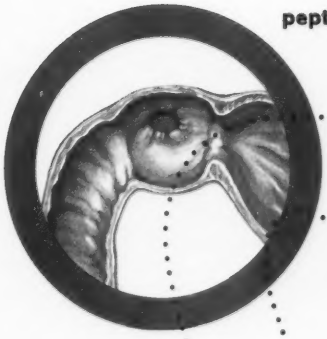


hiatus hernia

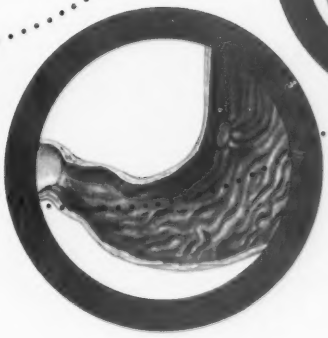
esophagitis



gastritis



peptic ulcer



gastric ulcer

in gastritis
topical anesthetic relieves

gastric discomfort

oxethazaine topically anesthetizes the mucosa in both the acid stomach and alkaline esophagus

- **new OXAINE M minimizes risk of constipation—** Palatable and well tolerated OXAINE M promotes good patient cooperation and comfort.

THERAPEUTIC EFFICACY IN CLINICAL TRIALS

in gastritis[1], esophagitis[2], peptic ulcer[3,4], irritable bowel syndrome[5] and related disorders

Schwartz and Spertus[6] used oxethazaine in alumina gel for hiatus hernia, esophagitis and gastritis in patients whose conditions were difficult to control without surgical intervention. Oxethazaine in alumina gel (with diet and anticholinergics) was significantly effective in these patients. The authors believe that surgery may often be avoided by the use of OXAINE in these difficult gastrointestinal problems.

OXAINE and OXAINE M were used in a series of patients referred because of lack of success with conventional therapy for complicated gastrointestinal problems. Of 56 patients, good to fair response was reported with OXAINE and OXAINE M. "In all cases there was no lasting improvement until oxethazaine was added to the regimen."[3] OXAINE and OXAINE M were adjudged useful adjuncts to the medical management of peptic ulcer, gastroduodenitis and esophagitis, hiatus hernia, exaggerated gastrocolic reflex, and achalasia.

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References: 1. Deutsch, E., and Christian, H.J.: J. Am. Med. Assoc. *169*:2012 (April 25) 1959. 2. Jankelson, I.R., and Jankelson, O.M.: Am. J. Gastroenterol. *32*:636 (Nov.) 1959. 3. Moffitt, R.E.: Rhode Island Med. J. *44*:151 (March) 1961. 4. Hollander, E.: Am. J. Gastroenterol. *34*:613 (Dec.) 1960. 5. Jankelson, O.M., and Jankelson, I.R.: Am. J. Gastroenterol. *32*:719 (Dec.) 1959. 6. Schwartz, I.R., and Spertus, I.: Scientific Exhibit, A.A.G.P., Miami Beach, April 16-20, 1961.

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For further information on limitations, administration and prescribing of OXAINE and OXAINE M, see descriptive literature or current Direction Circular.

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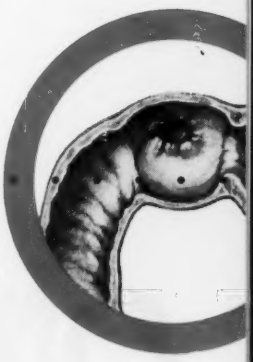
- inactivates pepsin and promotes healing
- avoids constipation and acid rebound



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sedative
anticholinergic

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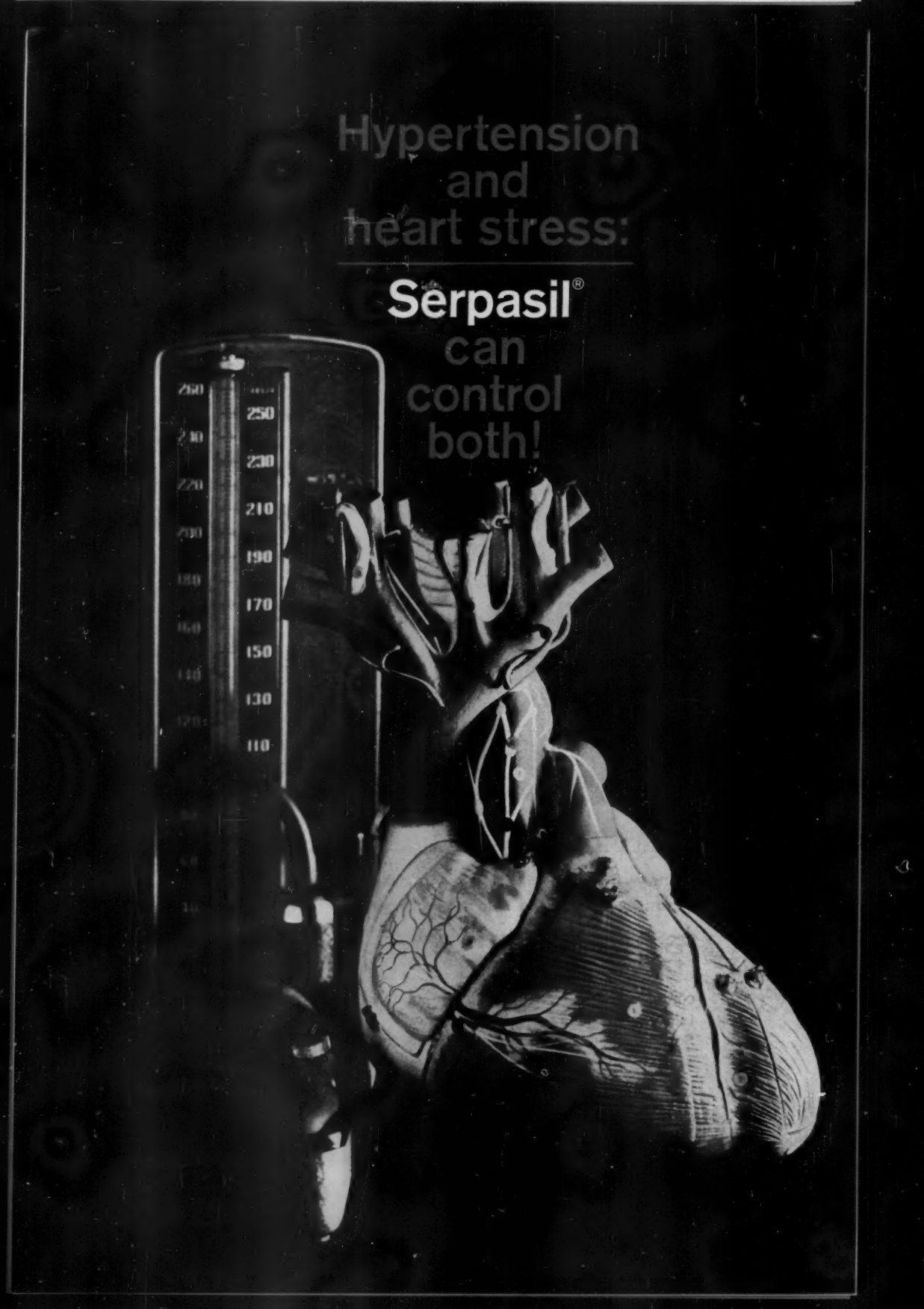
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Serpasil lowers blood pressure gently, guards against cardiac damage

Serpasil—in addition to its well-established effectiveness in controlling high blood pressure—offers an important bonus in treating hypertension. Laboratory studies show that Serpasil can prevent stress-induced heart damage,[1,2] presumably through its ability to deplete the catecholamines (epinephrine and norepinephrine) from the myocardium.[3,4]

These laboratory data are clinically significant in light of growing evidence[5-7] that more than purely "mechanical" overwork may be involved in cardiac damage associated with hypertensive disease. Raab[6] suggests that much of this damage is due to a direct metabolic action of the catecholamines on heart muscle. The way to prevent it, he believes, is to deplete or inactivate excess catecholamines.

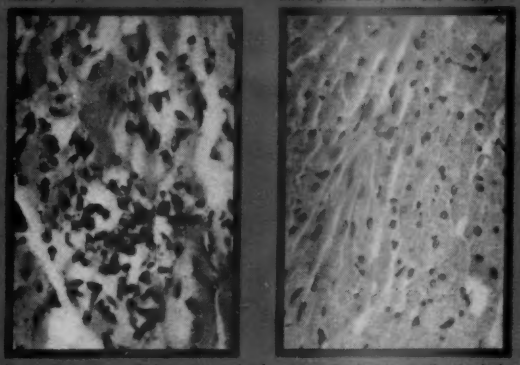
Thus, Serpasil not only eases the mechanical burden on the heart by reducing peripheral resistance and slowing heart rate, it may also provide protection against catecholamine-induced heart damage—the added benefit in prescribing Serpasil for hypertension.

References: 1. Raab, W., Stark, E., and Gigee, W. R.: Circulation 20:754 (Oct.) 1959. 2. Raab, W.: Research report to CIBA. 3. Carlsson, A., Rosengren, E., Sertler, A., and Nilsson, J.: Psychotropic Drugs (edited by Garattini, S., and Ghetti, V.), Elsevier Publishing Company, Amsterdam, 1957, pp. 363-372. 4. Waud, D. R., Kottegoda, S. R., and Krayer, O.: J. Pharmacol. & Exper. Therap. 124:340 (Dec.) 1958. 5. Raab, W.: Am. J. Cardiol. 5:571 (May) 1960. 6. Bayer, O., Borden, N. E., Boeminghaus, H., and Ellert, S.: Ztschr. klin. Med. 148:607 (June) 1950. 7. Raab, W.: Hormonal and Neurogenic Cardiovascular Disorders, The Williams & Wilkins Company, Baltimore, 1953, pp. 457, 465.

LABORATORY EVIDENCE SHOWS SERPASIL PREVENTS STRESS-INDUCED HEART DAMAGE[2]

Severe heart damage in unprotected stressed rat. Tissue taken from rat given 2-α-methyl-9-α-fluorohydrocortisone and stressed (by restraint) for 15 hours. (Photomicrographs from Raab.[2])

No heart damage in stressed rat protected with Serpasil. Tissue taken from rat given 2-α-methyl-9-α-fluorohydrocortisone and stressed as at left, but also given Serpasil (0.4 microgram daily for one week).



Note: While Serpasil did not completely protect the hearts of all animals in this study, it greatly reduced myocardial damage in most of them. Original magnification of photomicrographs: approximately 450 X.

Complete information about indications, dosage, cautions, and side effects of Serpasil—as well as a full report on its heart-protecting action—will be sent on request.

SUPPLIED: Tablets, 0.1 mg., 0.25 mg. (scored) and 1 mg. (scored).

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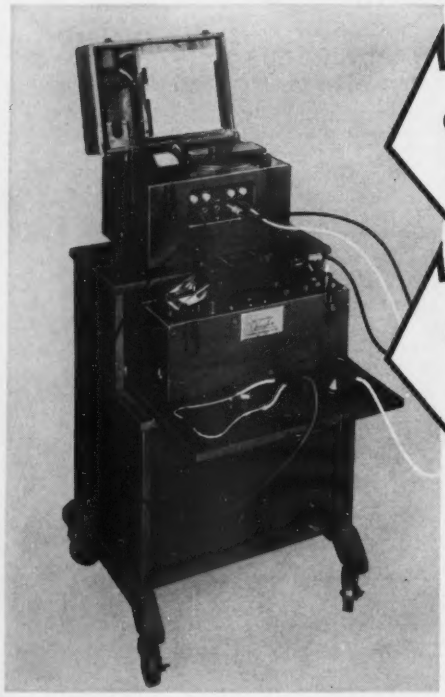

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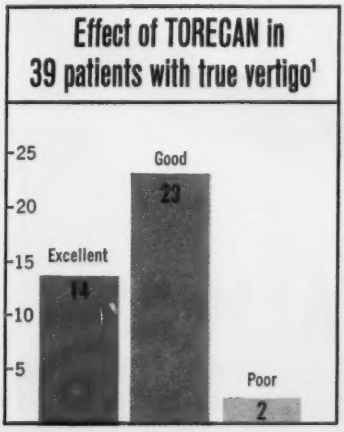

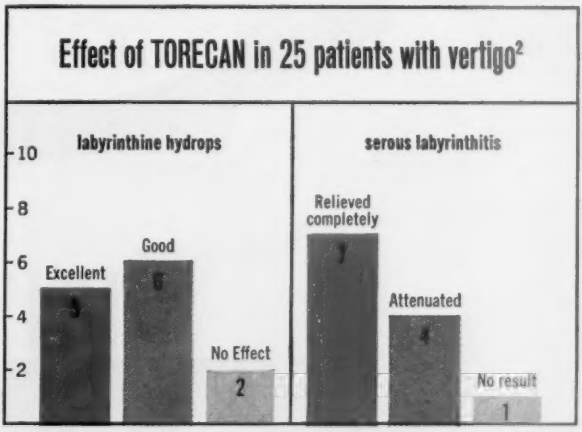

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AVERAGE ADULT DOSAGE: **Oral:** 1 tablet (10 mg.) three times daily.
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PRECAUTIONS: It is obvious that sound clinical judgment must be exercised in determining whether vomiting represents a warning of organic abnormality and that this must first be recognized before employing a potent antiemetic such as Torecan.

Drowsiness and/or dryness of the mouth may occur with doses above 30 mg. daily. While no hepatic, hematopoietic or renal toxicity have been reported at recommended dose levels, it should be remembered that these are reactions which may occur with the phenothiazine group. Orthostatic hypotension may be manifested at higher dose levels. Torecan is contraindicated in severely depressed or comatose states from any cause. In excessive doses, Torecan may produce extrapyramidal stimulation with the varied symptom complex characteristic of this complication. Ampuls are recommended for **intramuscular injection only.**

1. Kearby, N.: Thiethylperazine dimaleate in the treatment of vertigo, presented at Louisiana State Medical Society, New Orleans, May 10, 1961.
2. Rubin, W.: Clinical evaluation of Torecan in the treatment of vertigo, to be published.

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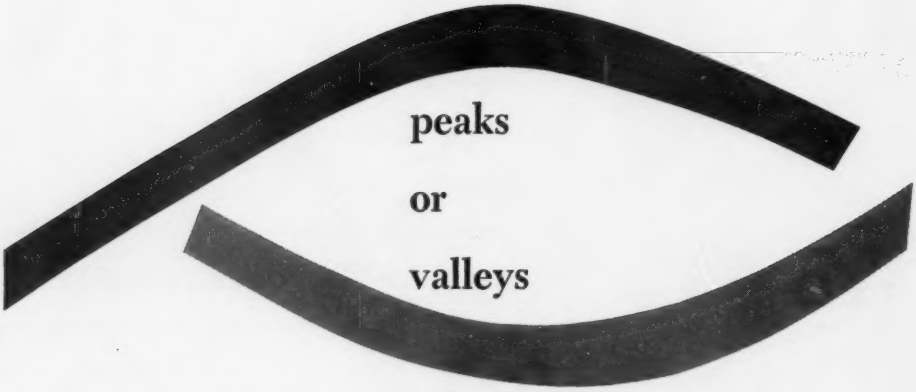

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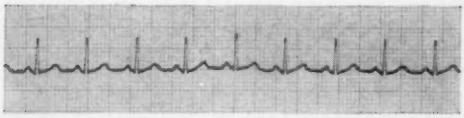

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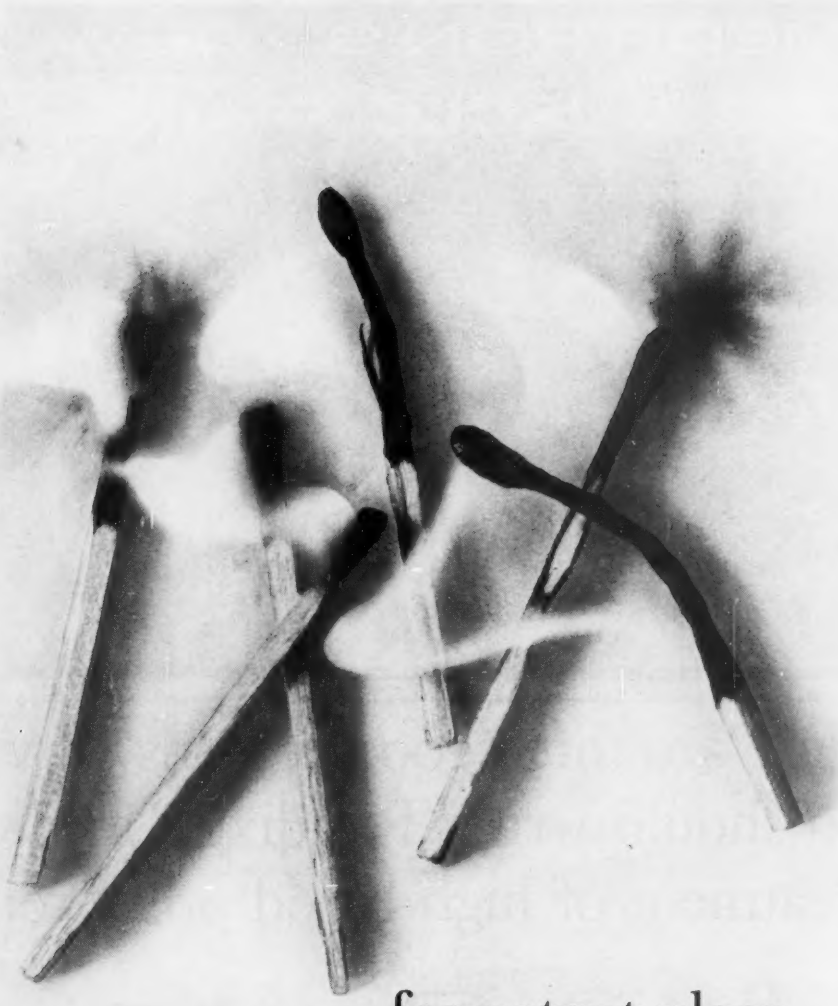

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to relieve tensions and to inhibit
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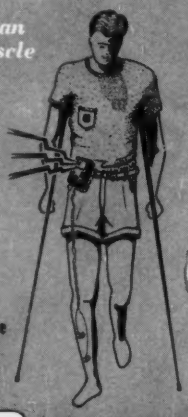

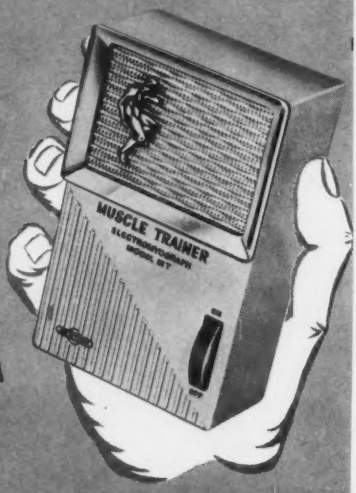

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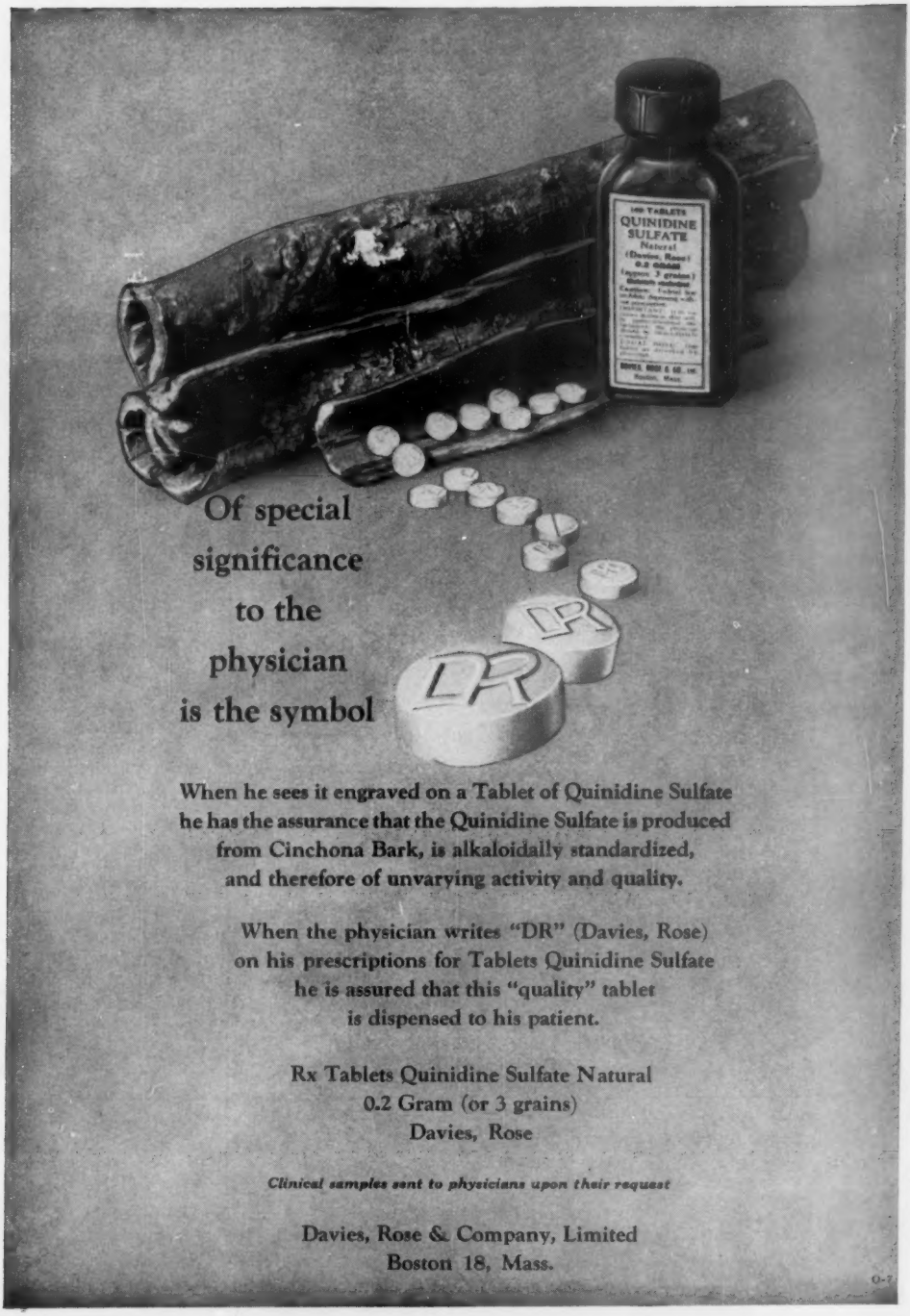
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CLINICAL USE CONFIRMS EFFICACY

SPARINE has been proved highly effective in management of acute manifestations of severe mental and emotional disturbances. Rapid control of psychotic behavior is quickly achieved by IV or IM administration. Follow-up maintenance therapy is usually obtained with tablets or syrup. The following abstracts from important clinical studies further testify to the usefulness of SPARINE.

in acute alcoholic intoxication

Figurelli[1] noted that the use of SPARINE in cases of acute alcoholism controlled symptoms of active delirium, as well as nausea and vomiting, and reduced mortality rates. According to Figurelli "... medication with promazine [SPARINE] enables more rapid control of delirium, eliminates the prolonged and more expensive therapeutic measures which formerly were the only recourse ... and permits earlier return of the patient to gainful occupation." Parenteral SPARINE was usually used initially by Figurelli; oral SPARINE was used for maintenance. No precipitous drop in blood pressure occurred in the series of patients studied by Figurelli.

Note: The degree of central nervous system depression induced by SPARINE has not been great; however, in the acutely inebriated person the initial dose should not exceed that recommended to be sure that the depressant effect of alcohol is not enhanced. SPARINE should not be used in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates, etc.). In patients with cerebral arteriosclerosis, coronary heart disease, or other conditions where a drop in blood pressure may be undesirable, SPARINE should be used with caution.

in acute behavior disorders

Fink and Vlavianos[2] reported that with SPARINE "*Violence* and *acute overactivity* were minimized, and combativeness was reduced. The patients became more co-operative." SPARINE did not impair mental acuity. Insomnia was reduced in all overactive patients. Patients with hallucinations or delusions generally improved as long as medication was continued. Acute hallucinations were quickly relieved. At the end of these studies of 200 ward patients: 37 were released; 41 were transferred to an open ward with privileges and were being considered for release. No side effects were observed.

for patients reacting adversely to other ataraxics

SPARINE was used[3] to treat chronic hospitalized psychotic patients ranging in age from 16 to 88 years. Improvement was noted in 72 percent of 180 patients treated. Psychotherapy was facilitated so that 26 patients were able to be released from the hospital. Of 58 patients who were placed on SPARINE because of complications resulting from other ataraxic therapy, 49 (85 percent) showed resolution of complications and were able to be maintained on SPARINE.

References: 1. Figurelli, F.A.: J. Am. Med. Assoc. *166*:747 (Feb. 15) 1958. 2. Fink, L., and Vlavianos, G.: Psychiat. Quart. *32*:532 (July) 1958. 3. Graffeo, A.J.: Am. J. Psychiat. *116*:842 (March) 1960.

For further information on limitations, administration, and prescribing of SPARINE, see descriptive literature or current Direction Circular.

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"...our studies indicate that ulcer pain in the uncomplicated case is invariably associated with abnormal motility."[2]

A groundswell of medical opinion now indicts gastric spasm—as well as acid—in the causation of ulcer pain.[1-6]

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antispasmodic: BENTYL (dicyclomine) Hydrochloride *antacids:* Magnesium Oxide/Aluminum Hydroxide Gel *demulcent:* Methylcellulose *anti-enzyme:* Sodium Lauryl Sulfate

References: 1. Altschule, M. D.: M. Sc. *6*:560, 1959. 2. Ruffa, J. M.; Boylin, G. J.; Legerton, C. W., and Texter, E. C., Jr.: Gastroenterology *23*:252, 1953. 3. Texter, E. C., *et al.*: Ann. Int. Med. *51*:1275, 1959. 4. Kusich, A. M.; Boleman, A. P., Jr., and Rafsky, J. C.: Am. J. Digest. Dis. *1*:361, 1956. 5. Roth, J. L. A.; Wechsler, R. L., and Bockus, H. L.: Gastroenterology *31*:493, 1956. 6. Rafsky, J. D.: Gastroenterology *27*:39, 1954.

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the antidepressant with a significant difference:

• given orally or parenterally, ELAVIL provides PROMPT relief of associated anxiety, tension, and insomnia • followed by control* of underlying depression

*Some depressed patients respond within 5 to 10 days, while others may require up to two weeks or longer to obtain benefit.

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- a single agent (not a combination of compounds)
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- may be used in ambulatory or hospitalized patients
- not an amine oxidase (MAO) inhibitor

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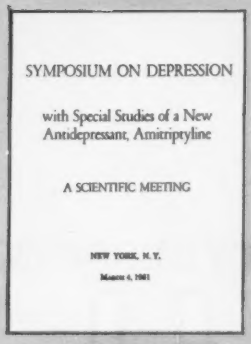


EXCERPTS FROM A SYMPOSIUM ON DEPRESSION

ELAVIL®

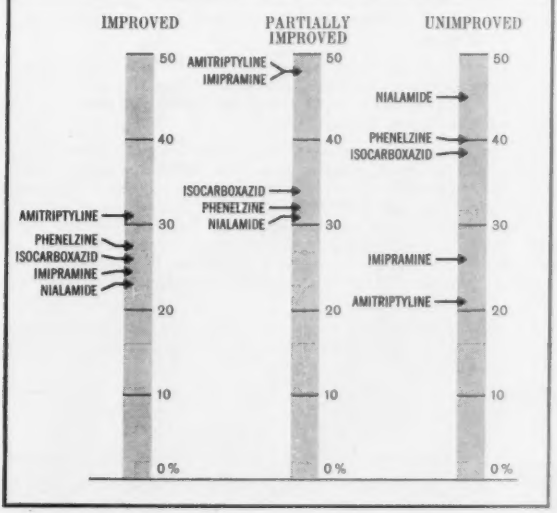
AMITRIPTYLINE HYDROCHLORIDE

INVESTIGATOR	FINDINGS
DUNLOP, EDWIN: The treatment of depression in private practice.	"Amitriptyline [ELAVIL] has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears . . . to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes. "... Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders."
BENNETT, DOUGLAS: Treatment of depressive states with amitriptyline.	"In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation. The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression."
SAUNDERS, JOHN C.: Antidepressives: the pith of affective therapy.	"Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuropsychiatric diseases. . . . Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75)."
OSTFELD, ADRIAN M.: Effects of an antidepressant drug on tests of mood and perception.	"Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population."

(This symposium was published in Diseases of the Nervous System, Volume 22, Section Two—Supplement, May 1961)

INVESTIGATOR	FINDINGS
AYD, FRANK J., JR.: A critique of antidepressants.	"Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine. "... Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments."

COMPARISON OF THERAPEUTIC RESULTS WITH VARIOUS ANTIDEPRESSANTS



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EXCERPTS FROM A SYMPOSIUM ON DEPRESSION (continued)

ELAVIL®

AMITRIPTYLINE HYDROCHLORIDE

INVESTIGATOR	FINDINGS
DORFMAN, WILFRED: Masked depression.	"In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%)."
FELDMAN, PAUL E.: Psychotherapy and chemotherapy (amitriptyline) of anergic states.	"Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings."

INDICATIONS: manic-depressive reaction—depressed phase; involutional melancholia; reactive depression; schizoaffective depression; neurotic-depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whether the emotional difficulty is a manifestation of neurosis or psychosis,[1] and in ambulatory or hospitalized patients.[1,2,3]

USUAL ADULT DOSAGE: Tablets – initial dosage 25 to 50 mg. three times a day, depending on body weight, severity, and clinical disturbances. Dosage may be adjusted up or down depending upon the response of the patient. Some patients improve rapidly, although many depressed patients require four to six weeks of therapy before obtaining antidepressant response. For the ambulatory patient the dosage range for Tablets ELAVIL is 40 to 150 mg. daily. In the hospitalized patient, a daily dosage up to 300 mg. may be required. Injection ELAVIL may be given IM to rapidly calm depressed patients with symptoms of anxiety and tension while instituting therapy of the underlying depression. Initial therapy is 2 to 3 cc. (20 to 30 mg.) IM, q.i.d.

The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. It does, however, augment or may even potentiate the action of MAO inhibitors. Thus, in patients who have been receiving MAO inhibitors, ELAVIL should be instituted cautiously after the effects of the MAO inhibitors have been dissipated. No evidence of drug-induced jaundice, agranulocytosis, or extrapyramidal symptoms has been noted. Side effects with ELAVIL are seldom a problem and are not serious. They are dosage-related and have been readily reversible. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma, prostatic hypertrophy and urinary retention.

SUPPLY: Tablets, 10 mg. and 25 mg., in bottles of 100 and 1000. **Injection** (intramuscular), in 10-cc. vials, each cc. containing 10 mg. amitriptyline hydrochloride, 44 mg. dextrose, 1.5 mg. methylparaben, 0.2 mg. propylparaben, and water for injection q.s.

REFERENCES: 1. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 2. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 3. Barse, J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

Before prescribing or administering ELAVIL, the physician should consult the detailed information on use accompanying the package or available on request.

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Capla is effective alone in the treatment of mild to moderate hypertension, and can be combined with diuretics or peripherally acting antihypertensives in more severe cases.

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Capla acts rapidly, producing substantial blood pressure reduction within two hours, yet does not produce postural hypotension. It has proved exceptionally well tolerated in clinical use and has no known contraindications. Capla has not produced changes in renal, hematological, hepatic or endocrine function.

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Hypertensive patients with other disorders can receive Capla along with other medications.

For example, patients with congestive heart failure, angina, and diabetes mellitus can receive Capla along with such medications as digitalis, nitrates, and insulin—without aggravating these other disorders.

a new drug that works in a new way without serious side effects

Capla lowers blood pressure without serious side effects

In 755 hypertensive patients treated with Capla, the only side effect observed with any frequency was mild, usually transient, drowsiness.

Capla is effective therapy without the unpleasant and serious side effects which often cause patients to abandon treatment. Side effects, when they do occur, are mild and usually transient. Transient drowsiness sometimes occurs, usually at higher dosage.

Patients on Capla often report a mild calming effect which, together with Capla's unusual freedom from side effects, makes therapy gratifying for both patient and physician.

Effective in clinical use

Average reductions in systolic and diastolic blood pressure reported with Capla. (755 patients)

	BEFORE	AFTER
MILD (403 patients) (Diastolic B.P. up to 100 mm. Hg)	183/93	159/85
MODERATE (249 patients) (Diastolic B.P. from 101 to 115 mm. Hg)	187/108	169/94
SEVERE (103 patients) (Diastolic B.P. over 116 mm. Hg)	208/120	162/99

Usual dose, Capla 300 mg., q.i.d.—duration of therapy, 3 weeks to over 1 year. These data show Capla reduces both systolic and diastolic pressure, usually in proportion to initial pre-treatment elevations.

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Composition: Each white, scored tablet is 300 mg. of Capla (mebutamate, Wallace).
Supplied: Bottles of 100 tablets.

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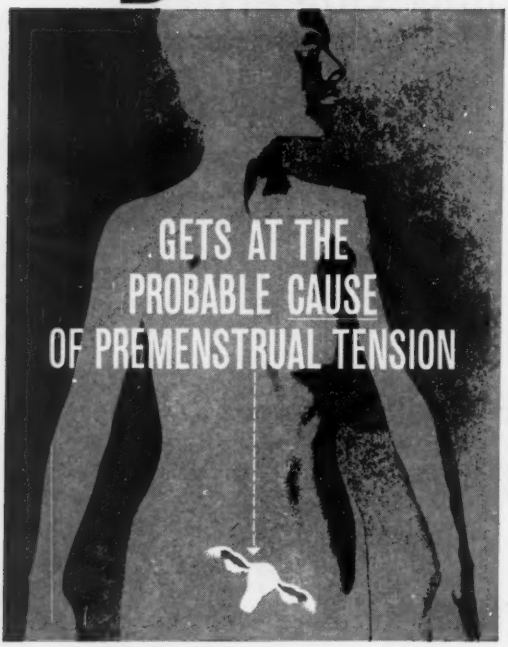

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Each tablet contains:

Provera (medroxyprogesterone acetate)	2.5 mg.
Cardrase (ethoxzolamide)	35 mg.
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Supplied: As layered tablets in bottles of 20 and 100.

Precautions: Side effects following the use of Cȳtran are rare. The patient should be observed for possible sensitivity to one or more of the components. Drowsiness, if seen, may be relieved by decreasing the dosage.

Contraindications: Cȳtran should not be used in patients with abnormal uterine bleeding until malignancy and all other organic pathologic conditions have been ruled out. Carbonic anhydrase inhibitors should not be administered in the presence of renal failure, hyperchloremic acidosis, Addison's disease, or any condition involving depressed sodium and/or potassium levels. Caution must be observed in the presence of symptomatic hepatic cirrhosis as acidosis may develop. Tranquilizing agents, generally, are not indicated in true depressive states without concomitant anxiety.

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References: 1. David, N. A.; Porter, G. A.; and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Fuchs, M.; Moyer, J. H.; and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 3. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

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Use Levophed first to be sure

Most dependable vasopressor available[1]

Elevates blood pressure when others fail[2]

Increases coronary blood flow as much as 500 per cent[3]

Safer because it is controllable at all times[4]

Doubles the survival rate in coronary shock[5]

New, simple protection against possible skin damage[2]

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References: 1. Heller, E. M.: *Canad. M.A.J.* 82:917, April 30, 1960. 2. Zucker, Gary; Eisinger, R. P.; Floch, M. H., and Singer, M. M.: *Circulation* 22:935, Nov., 1960. 3. Williams, J. H., and Corday, Eliot: *Dis. Chest* 35:561, May, 1959. 4. Corday, Eliot, and others: *Ann. Int. Med.* 50:535, March, 1959. 5. Miller, A. J., and Moser, E. A.: *J.A.M.A.* 169:2000, April 25, 1959.

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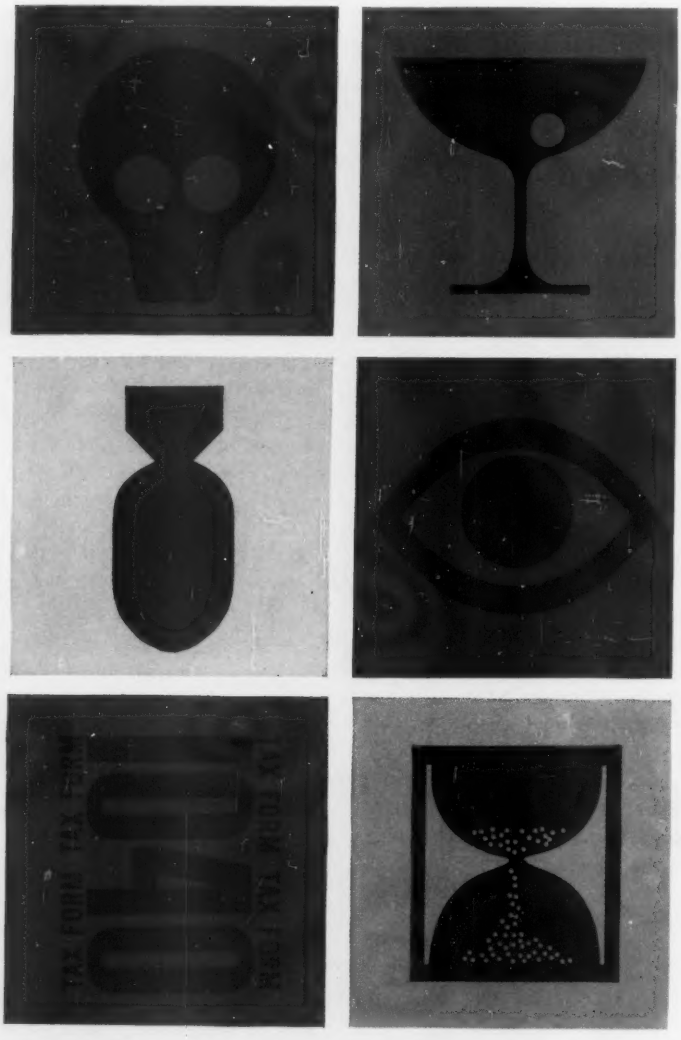

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References:

[1]Bastian, J. W.: Classification of CNS Drugs by a Mouse Screening Battery. To be published in Intern. Arch. de Pharmacodynamie; [2]Hubata, J. A., and Hecht, R. A.: Review of Clinical Use of Hydroxyphenamate (Listica) in 1,759 Patients. To be published in Clinical Medicine; [3]Taub, S. J.: Management of Anxiety in Allergic Disorders—New Approach. To be published in Psychosomatics; [4]Cahn, B.: Experience with a New Tranquilizing Agent (Hydroxyphenamate). *Ibid;* [5]Davis, O. F.: On Use of Hydroxyphenamate in Anxiety Associated with Somatic Disease. To be published; [6]Alexander, L.: Effect of Hydroxyphenamate on Conditional Psychogalvanic Reflex in Man. Supplement to Diseases of the Nervous System, Sept., 1961; [7]Cahn, B.: Effect of Hydroxyphenamate in Treatment of Mild and Moderate Anxiety States. *Ibid;* [8]Cahn, M. M., and Levy, E. J.: Use of Hydroxyphenamate (Listica) in Dermatological Therapy. *Ibid;* [9]Eisenberg, B. C.: Amelioration of Allergic Symptoms with a New Tranquilizer Drug (Listica). *Ibid;* [10]Friedman, A. P.: Pharmacological Approach to Treatment of Headache. *Ibid;* [11]Greenspan, E. B.: Use of Hydroxyphenamate in Some Forms of Cardiovascular Disease. *Ibid;* [12]Gouldman, C., Lunde, F., and Davis, J.: Clinical Trial of Hydroxyphenamate in Alcoholic Patients. *Ibid;* [13]McLaughlin, B. E., Harris, J., and Ryan, E.: Double Blind Study Involving "Listica," Chlordiazepoxide, and "Placebo" as Adjunct to Supportive Psychotherapy in Psychiatric Clinic. *Ibid;* [14]Bastian, J. W.: Pharmacology and Toxicology of Hydroxyphenamate. *Ibid;* [15]Bossinger, C. D.: Chemistry of Hydroxyphenamate. *Ibid.*

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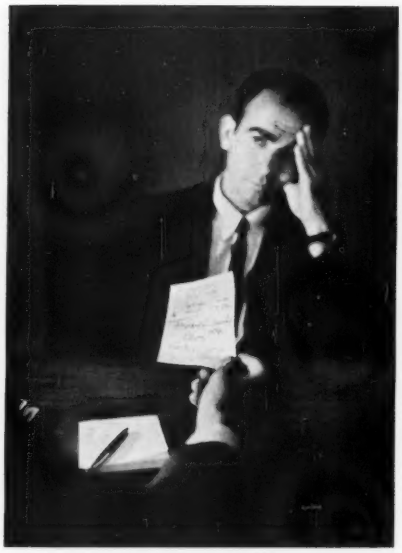

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*Jacques, A. A., and Fuchs, V. H.: J. Louisiana M. Soc. 113:200, May, 1961.

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References: 1. Rickels, K., *et al.*: J. Am. Med. Assoc. *171*:1649 (Nov. 21) 1959. 2. Appleby, B.P.: Brit. Med. J. *1*:391 (Feb. 6) 1960. 3. Pollak, M.: Practitioner *184*:231 (Feb.) 1960.

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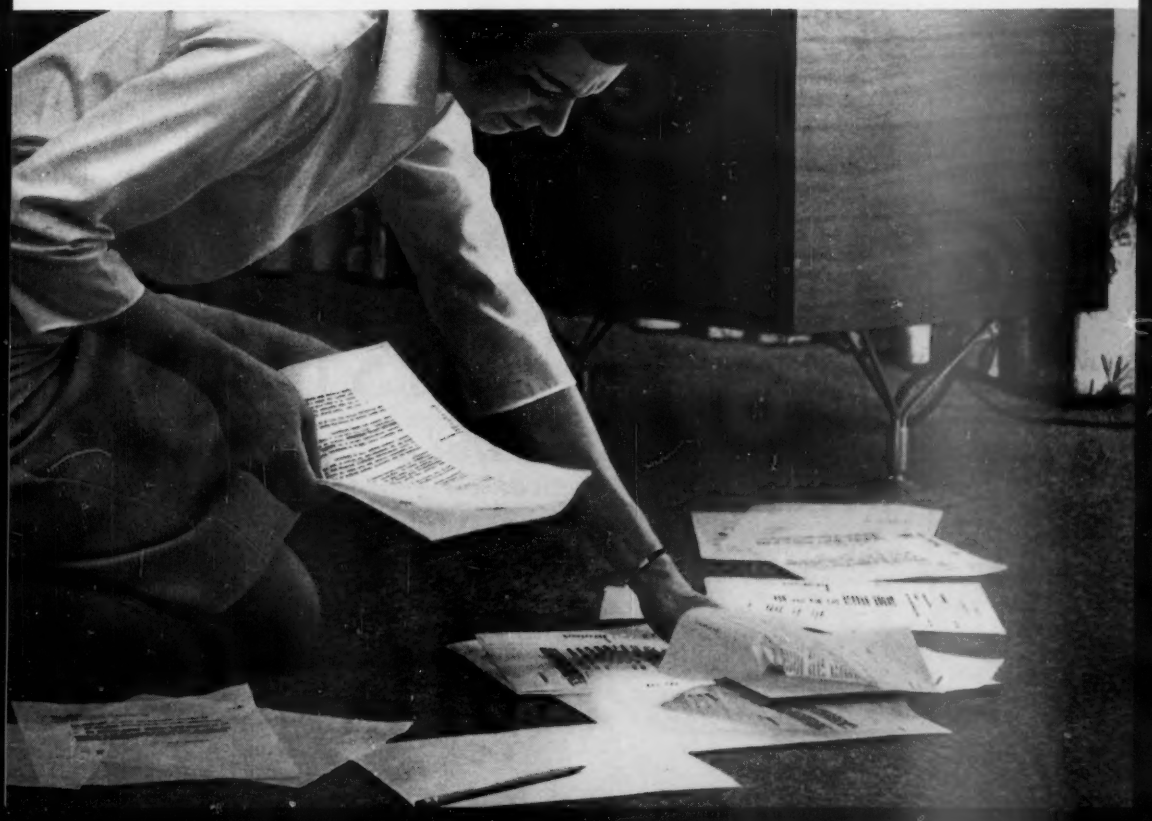

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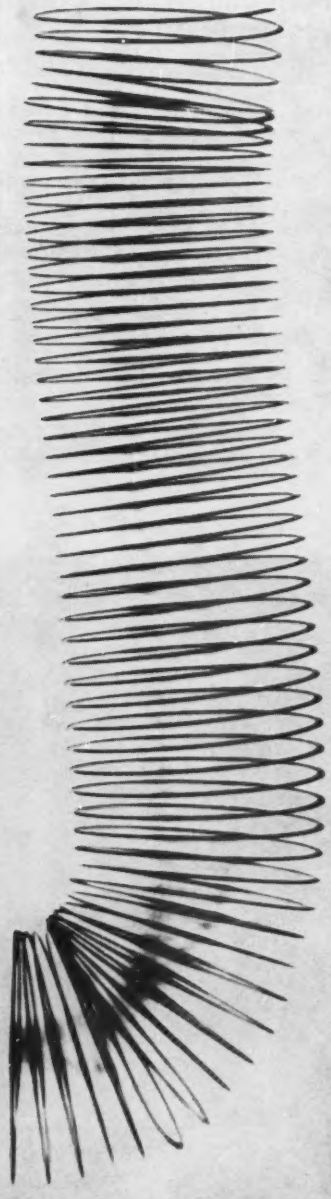
the diabetic with proteinuria!



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*Nagy El Mahallawy, M., and Sabour, M. S.: J.A.M.A. *173*:1783 (Aug. 20) 1960.

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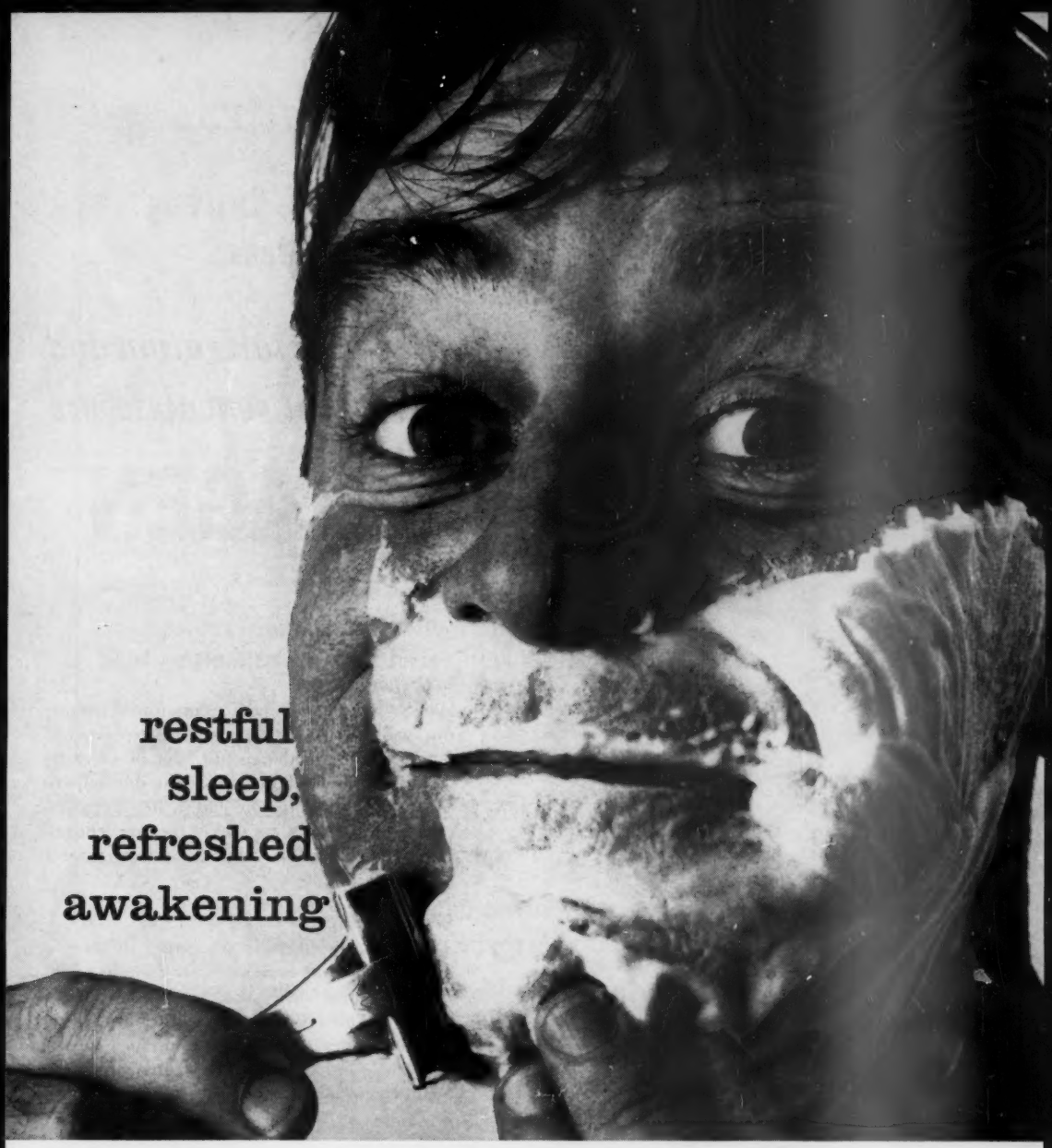

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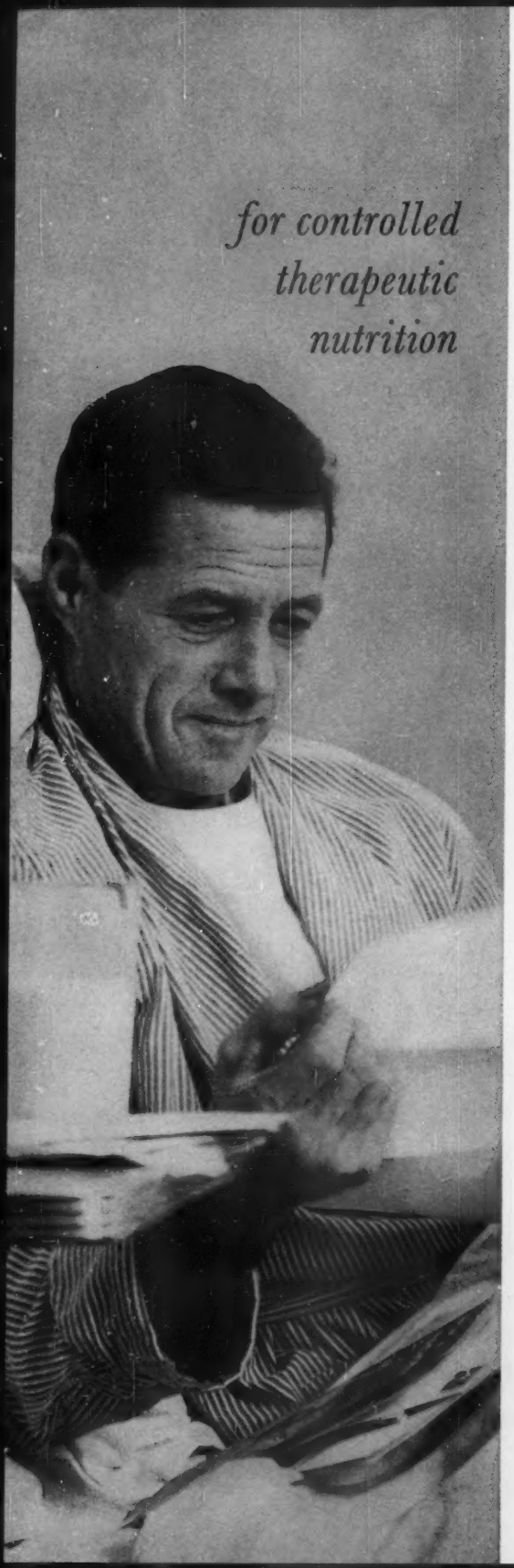

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references

(1) Pareira, M. D., *et al.*: J.A.M.A. *156*:810-816 (Oct. 30) 1954.
(2) Winkelstein, A.: Am. J. Gastroenterol. *27*:45-52 (Jan.) 1957.

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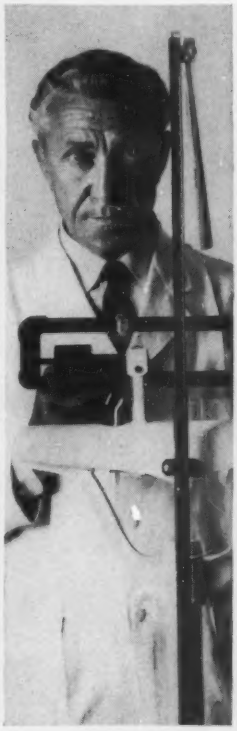

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Reference: 1. Bunim, J. J., in Hollander, J. L.: Arthritis and Allied Conditions, ed. 6, Philadelphia, Lea & Febiger, 1960, p. 364.

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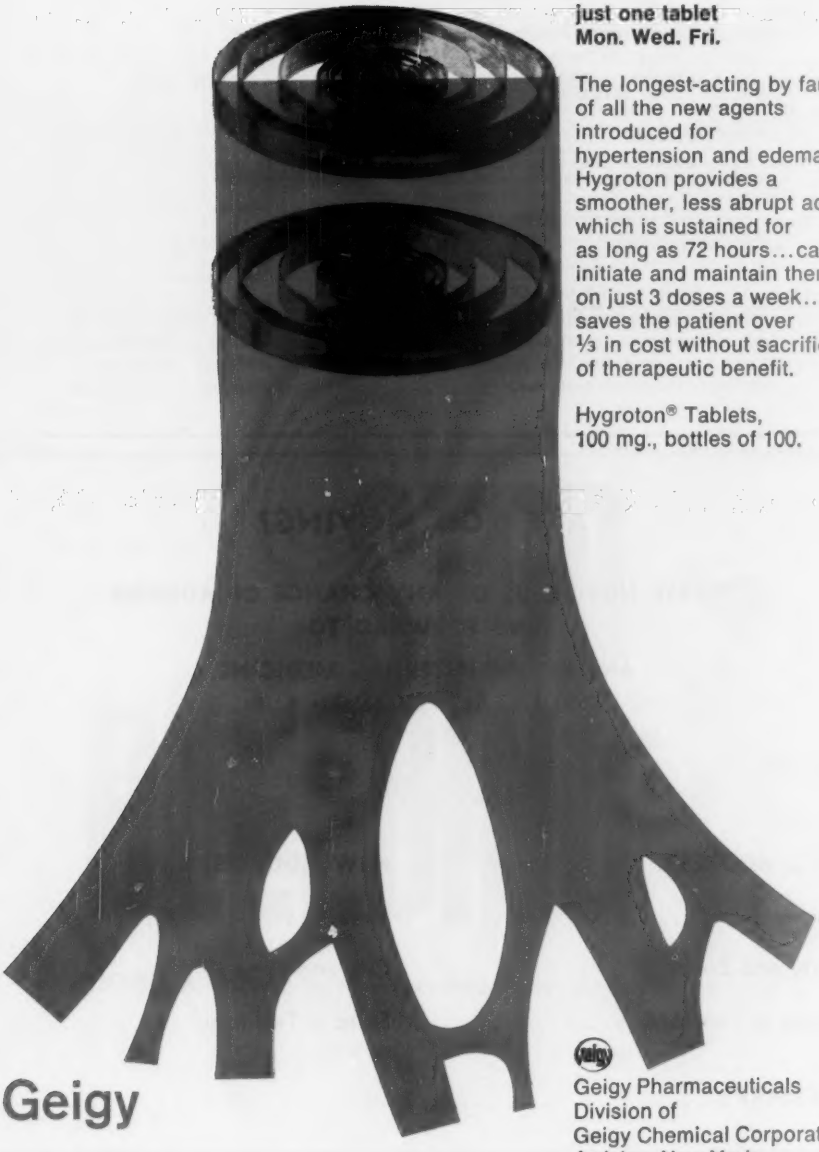

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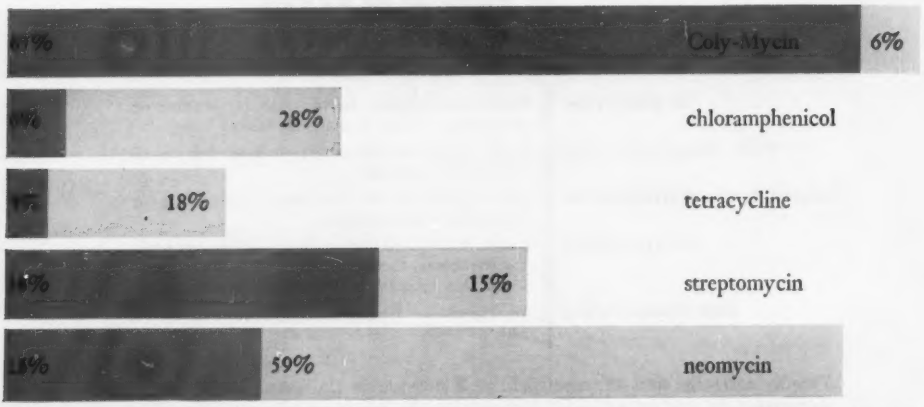

*Based on Meleney and Prout.[2]

1. Stamey, T. A., in Conn, H. F. (Ed.): Current Therapy 1961, Philadelphia, W. B. Saunders Company, 1961, p. 357.
2. Meleney, F. L., and Prout, G. R.: Surg. Gynec. & Obst. *112*:211, 1961.

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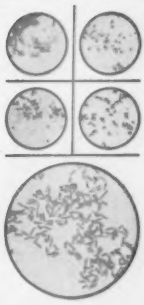

COLY·MYCIN®

THE ONLY BRAND OF COLISTIMETHATE SODIUM

INJECTABLE

Rapidly effective in acute or resistant gram-negative urinary infections, Coly-Mycin is also indicated in respiratory, surgical, wound, burn and blood stream infections due to sensitive organisms. Therapeutic blood levels and urine concentrations are quickly attained following deep intramuscular injection.

Exceptionally well tolerated at recommended dosage. No blood dyscrasia, moniliasis, renal or eighth nerve damage has been reported. Deep intramuscular injection causes little, if any, pain.

Primarily bactericidal against most gram-negative pathogens, including Pseudomonas and resistant strains of *E. coli* and *A. aerogenes* (not effective against Proteus). Coly-Mycin *rarely induces bacterial resistance.*

Full dosage information, available on request, should be consulted before initiating therapy. *For deep intramuscular injection only.* In vials containing 150 mg. colistin base as colistimethate sodium.

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GP1

New! For pain, distention and distress due to gastrointestinal gas!

Bloating, belching, borborygmus or flatulence—whatever the symptoms of gastrointestinal gas, Phazyme provides uniquely effective relief. Phazyme is the first comprehensive treatment for gastrointestinal gas that combines **both** digestive enzymes **and** gas-releasing agents—dual action that provides far better results than either agent alone. **Digestive enzymes** minimize gas formation resulting from digestive disorders or food intolerance. The gas-releasing agent, **specially activated dimethyl polysiloxane,** breaks down gas-enveloping membranes—prevents gas entrapment. A two-phase tablet, Phazyme releases these active components in the environments best suited to their actions—stomach or small intestine.

Phazyme is ideal medication for relieving gas distress in patients on the currently popular 900-calories-a-day diet. It is also recommended as routine therapy for cardiac patients to prevent gas from aggravating, complicating or simulating angina.

DOSAGE: One tablet with meals and upon retiring, or as required. SUPPLIED: As two-phase release, pink tablets, in bottles of 50 and 100.

REED & CARNRICK / Kenilworth, New Jersey R&C

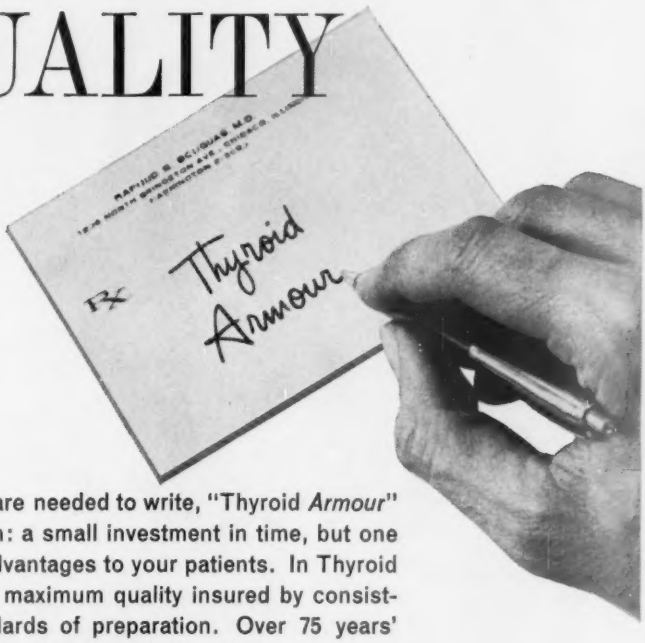
minimizes gas formation • prevents gas entrapment

PHAZYME™ TABLETS

When anxiety adds to the gas problem—

Phazyme with Phenobarbital The Phazyme formula with ¼ gr. phenobarbital. Supplied in bottles of 50. Phenobarbital may be habit forming.

only 2 seconds to specify maximum QUALITY



Only 2 seconds are needed to write, "Thyroid *Armour*" on a prescription: a small investment in time, but one that offers big advantages to your patients. In Thyroid *Armour* you get maximum quality insured by consistently high standards of preparation. Over 75 years' experience is behind the Armour brand.

THYROID U. S. P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (nontoxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger; potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz., 4 oz. and 1 lb. bottles.

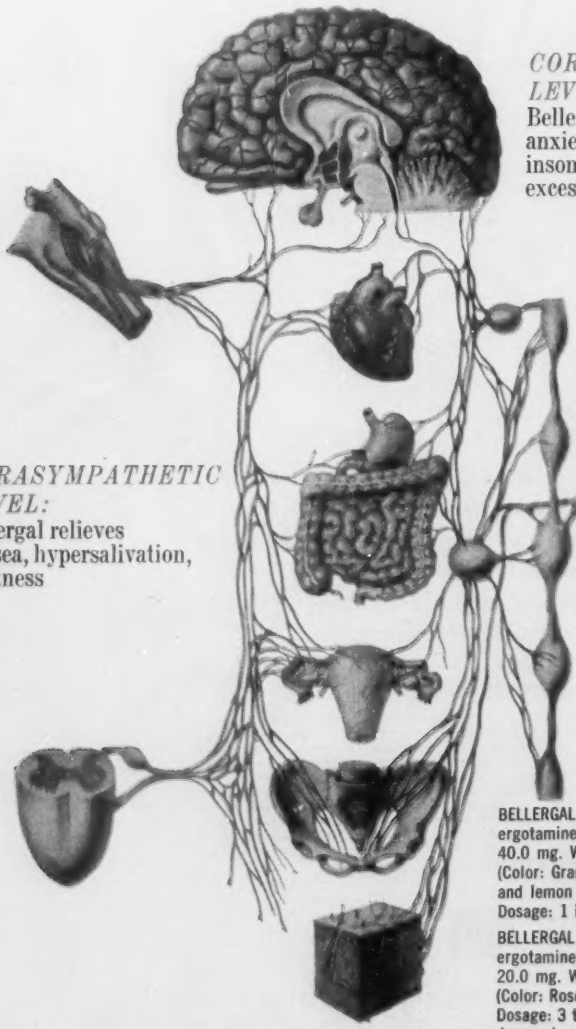
ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS • *Originators of Listica®*

Menopausal distress: a syndrome involving all three levels of the autonomic nervous system

for functional disorders of the menopause **Bellergal®** *SPACETABS®*

stabilizes the entire autonomic nervous system

(*without disturbing endocrine balance*)



CORTICAL LEVEL:
Bellergal relieves anxiety, irritability, insomnia, headache, excessive fatigability

SYMPATHETIC LEVEL:
Bellergal relieves hot flashes, palpitations, tachycardia, tremor, sweats

PARASYMPATHETIC LEVEL:
Bellergal relieves nausea, hypersalivation, faintness

SANDOZ

BELLERGAL SPACETABS—Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.) Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS—Bellafoline 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg. Warning: May be habit forming. (Color: Rose beige, sugar-coated.) Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.

Needed: a specific antibiotic
for a specific need
Prescribed: a Wyeth penicillin

WHEN CHILDHOOD ILLNESS CALLS FOR PENICILLIN

ORAL SUSPENSION

BICILLIN®

Benzathine Penicillin G, Wyeth

for children with penicillin-susceptible infections

- pleasant, cherry or custard flavor assures ready acceptance
- resists gastric destruction—high percentage of BICILLIN reaches duodenum, where absorption occurs
- in hemolytic streptococcal infections—300,000 units every 6 to 8 hours

Cherry flavor—300,000 units per 5 cc. teaspoonful, bottles of 2 fl. oz.
Custard flavor—150,000 units per 5 cc. teaspoonful, bottles of 2 fl. oz.

For further information on limitations, administration, and prescribing of BICILLIN, see descriptive literature or current Direction Circular. Wyeth Laboratories Philadelphia 1, Pa.

WHEN INFECTION CALLS FOR PROLONGED PENICILLIN ACTION

INJECTION

BICILLIN® Long-Acting

Benzathine Penicillin G, Wyeth

effective treatment of many upper respiratory infections

- produces blood levels lethal to most pathogens common in upper respiratory infections —streptococci, pneumococci, and penicillin-susceptible staphylococci
- produces prolonged blood levels, thus tending to prevent reinfection, relapse, or early recurrence
- eliminates streptococcus "carrier" state
- requires few injections . . . less trauma to patients
- affords TUBEX advantages—asepsis, less patient discomfort and ready-to-use convenience

Supplied: 1,200,000 units in TUBEX® sterile cartridge-needle unit (2-cc. size), pkgs. of 10; and in single-dose disposable syringe (2-cc. size). Also available in other strengths and sizes.

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Wyeth®

CALL ON THIS ORAL PENICILLIN FOR PROMPT, POTENT ANTIBIOTIC ACTION

PEN·VEE® K

Liquid: Penicillin V Potassium for Oral Solution, Wyeth
Tablets: Penicillin V Potassium, Wyeth

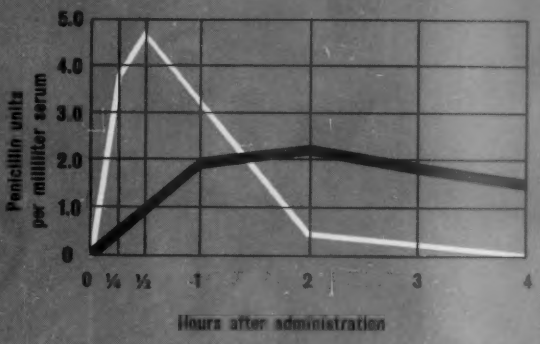
produces high penicillin blood levels

- easy-to-take Tablets or Liquid
- readily absorbed from the GI tract
- avoids pain, bother, and risk of injections
- palatable and well tolerated
- for all infections responsive to oral penicillin
- and for some usually requiring parenteral penicillin

A potent oral penicillin for high therapeutic efficacy

You can prescribe PEN•VEE K for any and all infections caused by penicillin-susceptible organisms. It is a reliable and predictable antibiotic. Demonstrable blood levels occur within 15 minutes after ingestion: peak blood levels within 30 minutes. PEN•VEE K is markedly effective for treatment and prophylaxis of common bacterial infections, including hemolytic streptococcal infections, certain staphylococcal infections, and pneumococcal and gonococcal infections.

Serum concentrations— oral and parenteral penicillin



Potassium penicillin V, 250 mg. (400,000 units)—one tablet. Average of 40 fasting subjects.[1]

Procaine penicillin G (600,000 units)—one injection. Average of 10 subjects.[2]

Palatable, convenient, well tolerated

PEN•VEE K is palatable, convenient (tablet or liquid), and well tolerated. These factors encourage good patient cooperation, which helps promote rapid recovery.

References: 1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-58, Medical Encyclopedia, Inc., p. 1004. 2. White, A.C., et al.: Antibiotics Annual 1955-56, Medical Encyclopedia, Inc., p. 490.

For further information on limitations, administration, and prescribing of PEN•VEE K, see descriptive literature or current Direction Circular.

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Wyeth®

because patients are more than arthritic joints...
controlling inflammatory symptoms is frequently not enough!

Even cortisone, with its severe hormonal reactions, can effectively control inflammatory and rheumatoid symptoms. But a patient is more than the sum of his parts – and the joint is only part of a whole patient. Symptomatic control is but one aspect of modern corticotherapy, because what is good for the symptom may also be bad for the patient.

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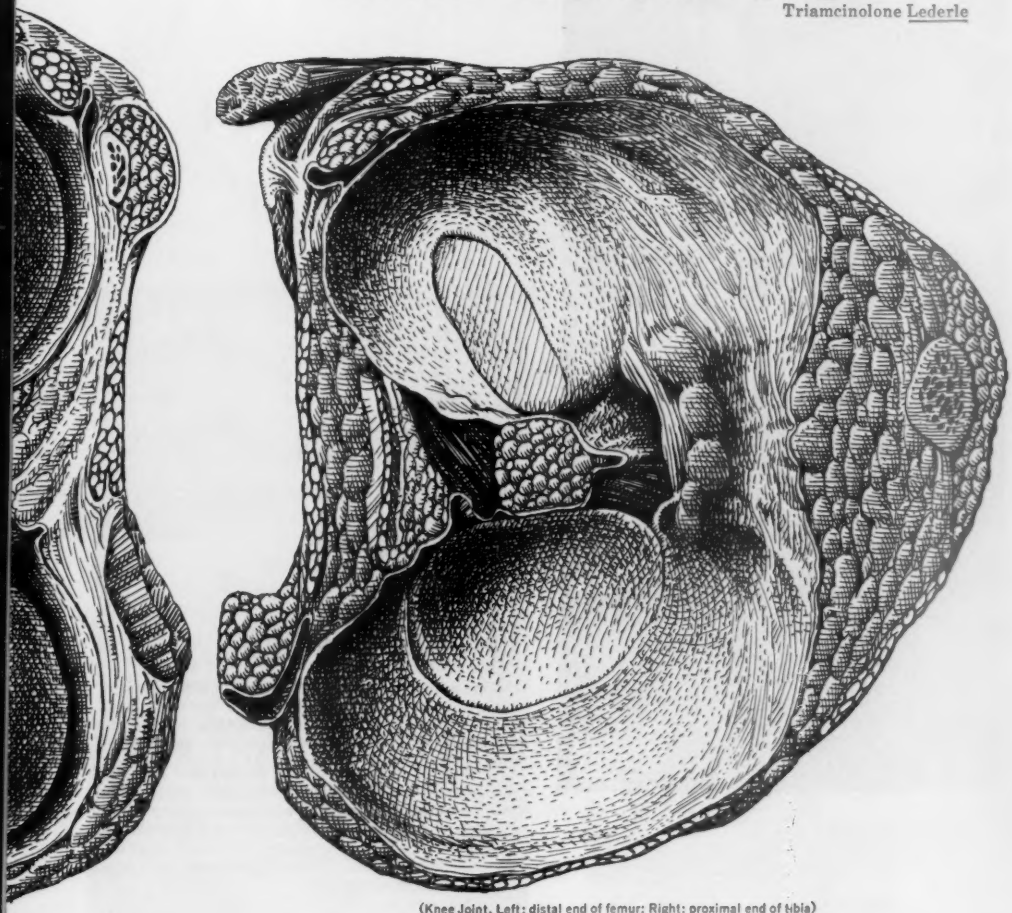
Unsurpassed "General Purpose" and "Special Purpose" Corticosteroid...
Outstanding for Short- and Long-Term Therapy

Aristocort®

Triamcinolone Lederle



(Knee Joint, Left: distal end of femur; Right: proximal end of tibia)

ARISTOCORT is an outstanding "special purpose" steroid when the complicating problem is increased appetite and weight gain, sodium retention and edema, cardiac disease, hypertension or emotional disturbance and insomnia.

ARISTOCORT provides unsurpassed anti-inflammatory control without sodium retention or edema – without the undesirable psychic stimulation and voracious appetite.

Supplied: Scored tablets (three strengths), syrup, parenteral and various topical forms. Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.

Lederle LEDERLE LABORATORIES • A DIV. OF AMERICAN CYANAMID COMPANY • PEARL RIVER, N. Y.

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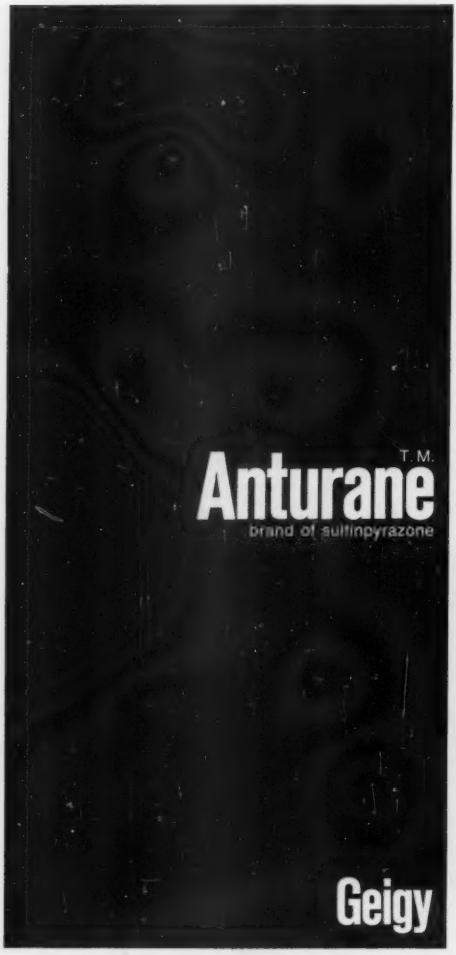


effectively checks the progress of gout by intensive, sustained, uricosuric action

In the long-term treatment of gout, the value of a uricosuric agent such as Anturane in preventing accumulation of the urate deposits responsible for chronic disability and joint derangement is well established.[1]

Clinical experience has demonstrated that Anturane not only prevents formation of new urate deposits, but with sustained therapy, also causes absorption of preexisting tophi.[2] With reduction in hyperuricemia, the incidence and severity of acute attacks are reduced,[3] the mobility of affected joints is improved,[4] and lingering joint pain is relieved.[2,4]

References: 1. Seegmiller, J. E., and Grayzel, A. I.: J.A.M.A. 173:1076, 1960. 2. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. 1:532, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. 17:326, 1958. 4. Gutman, A. B., and Yü, T. F.: Bull. New York Acad. Med. 34:287, 1958.

Full product information regarding dosage, side effects, precautions and contraindications available on request.

Anturane[T.M.], brand of sulfinpyrazone: Scored tablets of 100 mg in bottles of 100.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

AN 661-61

Put your low-back patient back on the payroll

Soma relieves stiffness —stops pain, too

YOUR CONCERN: Rapid relief from pain for your patient. Get him back to his normal activity, *fast!*

HOW SOMA HELPS: Soma provides direct pain relief while it relaxes muscle spasm.

YOUR RESULTS: With pain relieved, stiffness gone, your patient is soon restored to full activity—often in days instead of weeks.

Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days.* (*J.A.M.A. Vol. 172, No. 18, April 30, 1960.*)

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE:** 1 **TABLET Q.I.D.**

The muscle relaxant with an independent pain-relieving action

SOMA®

(*carisoprodol, Wallace*)

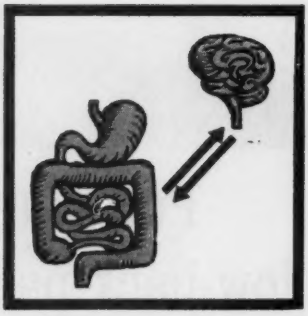
Wallace Laboratories, Cranbury, New Jersey

IN MANY GASTROINTESTINAL DISORDERS,

you may wish to try the simple measures first...dietary control, a good antacid, drastic reduction of smoking and drinking. Some of the less complicated gastrointestinal disorders will respond to this common-sense regimen. On the other hand, in many cases you will decide upon an anticholinergic. And while you're planning the over-all regimen, one conclusion probably becomes inescapable: any lasting improvement depends also on control of the emotional component.

FOR COMPREHENSIVE MANAGEMENT,

Librax combines two exclusive developments of Roche research in a single capsule: Librium, the successor to the tranquilizers and Quarzan, a superior new anticholinergic agent. Librax helps control the anxiety and tension so frequently associated with gastrointestinal disorders; does not cause diarrhea or other undesirable effects in the digestive tract. Quarzan offers effective antispasmodic-antisecretory action; produces fewer, less pronounced side reactions than other anticholinergic agents. Clinical trials have established the value of Librax specifically in the following conditions: peptic ulcer, gastritis, hyperchlorhydria, duodenitis, pylorospasm, ulcerative or spastic colitis, biliary dyskinesia, cardiospasm, and other functional or organic disorders of the gastrointestinal tract.



Each Librax capsule provides 5 mg Librium HCl and 2.5 mg Quarzan Br.

Consult literature and dosage information, available on request, before prescribing.

LIBRAX™

LIBRIUM® — 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide

QUARZAN® — 1-methyl-3-benziloyloxyquinuclidinium

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.

NEW
LIBRAX
CAUSE⇌EFFECT THERAPY

a pair of cardiac patients:

both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

▲ by mouth ▲ by needle ▲ by rectum

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.

KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY

Pemphigus vulgaris

SKIN DISORDERS

RESPONSIVE TO TRIAMCINOLONE

"Triamcinolone has been shown to have more profound anti-inflammatory and antiallergic properties than preceding corticosteroids."*

■ enhanced anti-inflammatory, antipruritic, antiallergic effects ■ less gastrointestinal distress ■ may be of value when other corticoids have failed ■ virtually no mood changes, edema, sodium or water retention, or secondary hypertension

Supply: Scored tablets of 1 mg., 2 mg. and 4 mg. Syrup, in 120 cc. bottles, each 5 cc. teaspoonful containing 5.1 mg. triamcinolone diacetate providing 4 mg. triamcinolone.

*Edelstein, A. J.: Pennsylvania M.J. 62:1831 (Dec.) 1959.

For full information, see your Squibb Product Reference or Product Brief. 'KENACORT'® IS A SQUIBB TRADEMARK.

Kenacort Squibb Triamcinolone

SQUIBB
Squibb Quality—the Priceless Ingredient

Can we measure the patient's comfort?

Not objectively, as activity of the heart can be measured electrocardiographically.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

Alphadrol*

Upjohn
75th year

See pages 18–19 for description indications, dosage, precautions side effects, and how supplied.

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*REG. U. S. PAT. OFF.—FLUPREDNISOLONE, UPJOHN

Fellowship Key

A charm, beautifully and expertly designed, bearing the seal of the College; wrought in 10K solid gold and embossed in the College colors. For Fellows only.

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Available also, in smaller size, as a fraternity pin with safety catch.

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The American College of Physicians
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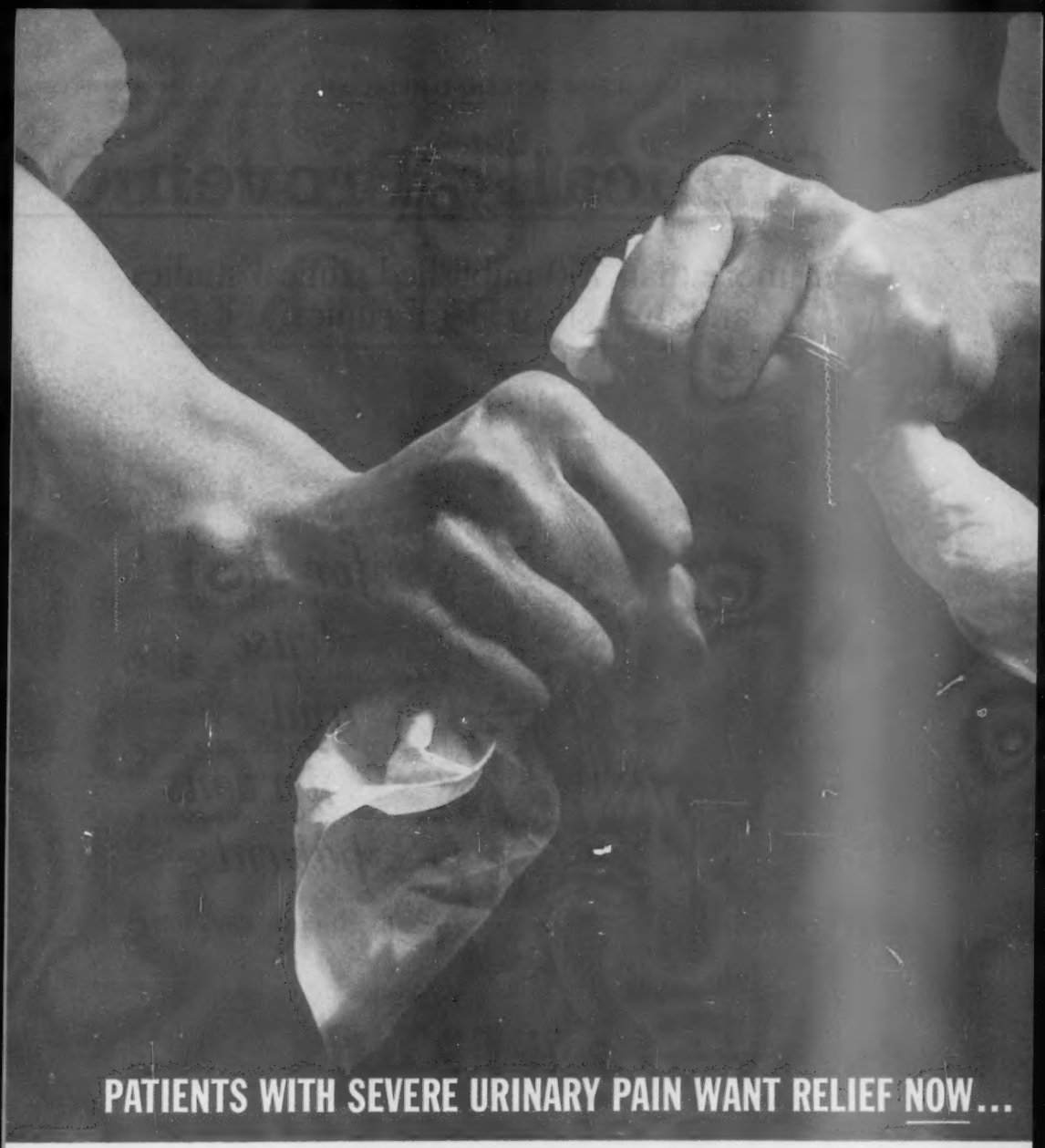
Philadelphia 4, Pa.



PATIENTS WITH SEVERE URINARY PAIN WANT RELIEF NOW...

Rx PYRIDIUM®

brand of phenazopyridine HCl

Two Pyridium tablets t.i.d. relieve the pain of urinary infection in only 30 minutes. During the first 3 to 4 days of therapy, Pyridium, prescribed along with any antibacterial of your choice, will make your patient comfortable until the antibacterial reduces inflammation and controls the infection.

AVERAGE DOSE: Adults—2 tablets t.i.d. Children 9 to 12 —1 tablet t.i.d. SUPPLIED: 0.1 Gm. tablets, bottles of 50. PRECAUTIONS: Pyridium is contraindicated in patients with renal insufficiency and/or severe hepatitis. *Full dosage information, available on request, should be consulted before initiating therapy.*

WARNER CHILCOTT

MORRIS PLAINS, N.J.

GP12

Makers of TEGRAL GELUSIL PROLOID PERITRATE HANDELAMINE

Clinically Proven

in more than 750 published clinical studies
and over six years of clinical use

for the tense and nervous patient

Miltown is a ***known*** drug and a dependable friend. Its few side effects have been fully reported. ***There are no surprises in store for either the patient or the physician.*** This is why, despite the appearance of "new and different" tranquilizers, meprobamate (Miltown) is prescribed more often than any other tranquilizer in the world.

Please Mention this Journal when writing to Advertisers

Outstandingly Safe and Effective

1 simple dosage schedule relieves anxiety dependably — without altering sexual function

2 does not produce ataxia

3 no cumulative effects in long-term therapy

4 does not produce Parkinson-like symptoms, liver damage or agranulocytosis

5 does not muddle the mind or affect normal behavior

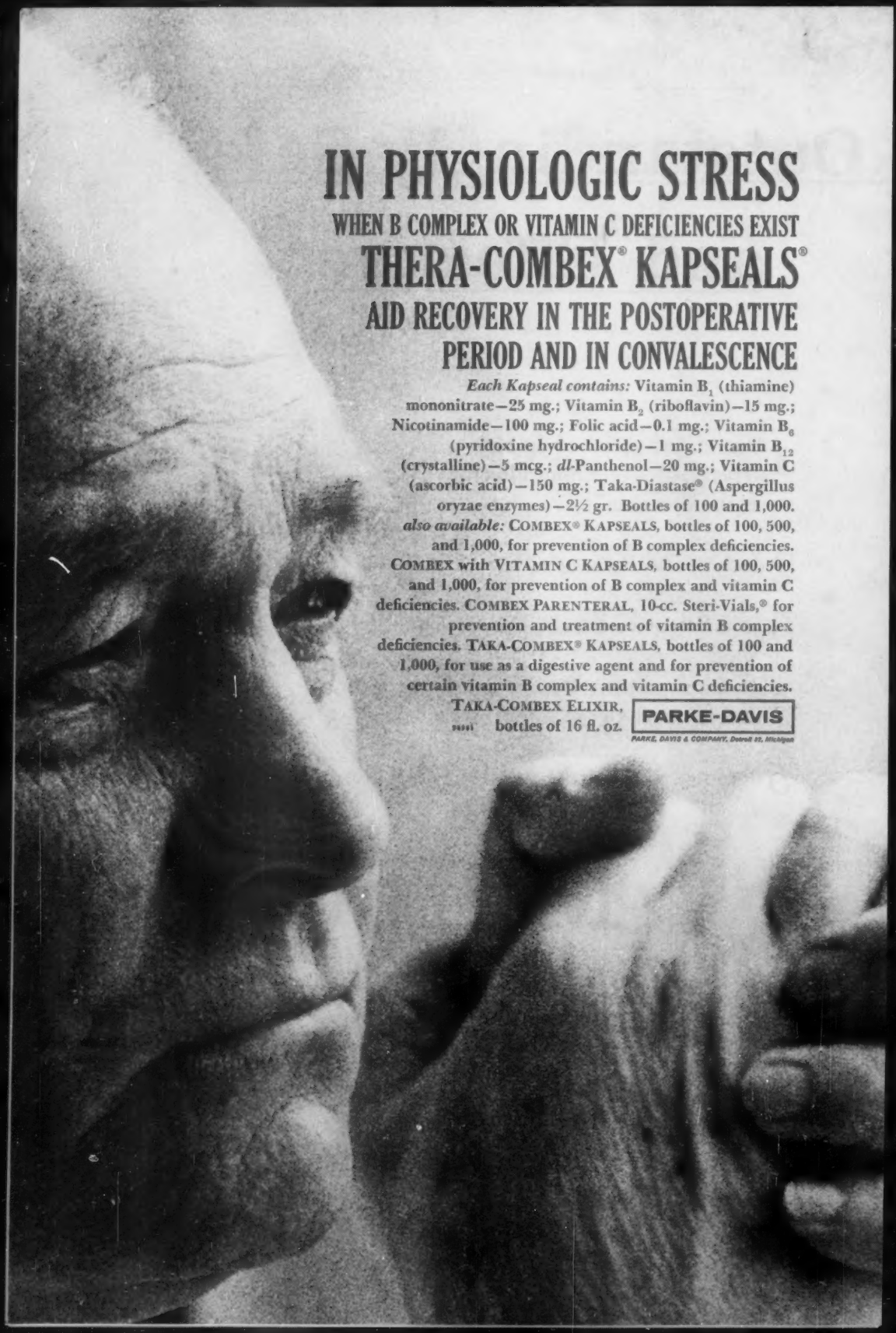
Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS®— 400 mg. *unmarked,* coated tablets; and in *sustained-release* capsules as MEPROSPAN©-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).

CM-5540

WALLACE LABORATORIES / *Cranbury, N. J.*



IN PHYSIOLOGIC STRESS

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THERA-COMBEX® KAPSEALS®

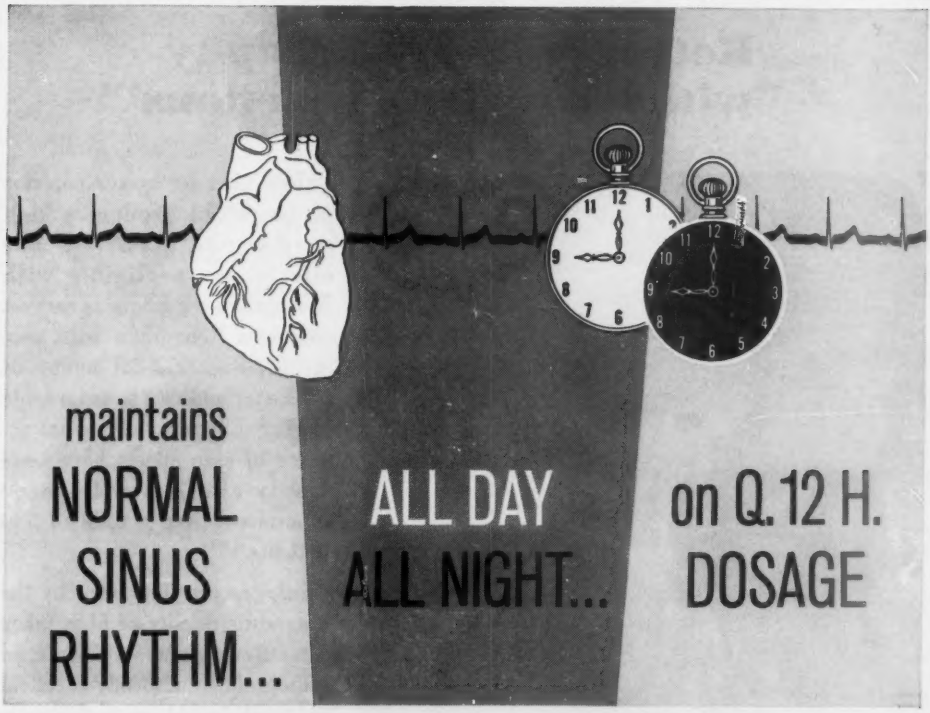
AID RECOVERY IN THE POSTOPERATIVE PERIOD AND IN CONVALESCENCE

Each Kapseal contains: Vitamin B_1 (thiamine) mononitrate—25 mg.; Vitamin B_2 (riboflavin)—15 mg.; Nicotinamide—100 mg.; Folic acid—0.1 mg.; Vitamin B_6 (pyridoxine hydrochloride)—1 mg.; Vitamin B_{12} (crystalline)—5 mcg.; *dl*-Panthenol—20 mg.; Vitamin C (ascorbic acid)—150 mg.; Taka-Diastase® (Aspergillus oryzae enzymes)—2½ gr. Bottles of 100 and 1,000.

also available: COMBEX® KAPSEALS, bottles of 100, 500, and 1,000, for prevention of B complex deficiencies. COMBEX with VITAMIN C KAPSEALS, bottles of 100, 500, and 1,000, for prevention of B complex and vitamin C deficiencies. COMBEX PARENTERAL, 10-cc. Steri-Vials,® for prevention and treatment of vitamin B complex deficiencies. TAKA-COMBEX® KAPSEALS, bottles of 100 and 1,000, for use as a digestive agent and for prevention of certain vitamin B complex and vitamin C deficiencies. TAKA-COMBEX ELIXIR, bottles of 16 fl. oz.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan



QUINAGLUTE®

DURA-TABS®

exclusive oral Sustained Medication*
Quinidine Gluconate 5 gr. (0.33 Gm.)

IN CARDIAC ARRHYTHMIAS[1-10]

Maximum efficacy: maintains effective quinidine blood levels all day, all night. **Better tolerated:** because quinidine gluconate is 10 times as soluble as the sulfate, and only part of daily Dura-Tab dosage contacts gastric mucosa. **Maximum convenience:** given q. 12 h.—no night dosage needed.

DOSAGE: for conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Dura-Tabs 3 or 4 times a day, for 2 to 3 days; longer periods are required in some patients. For maintenance, 1 or 2 Dura-Tabs q. 12 h. in most patients . . . Bottles of 30, 100 and 250 Quinaglute Dura-Tabs.

For SAMPLES and complete literature[1-10] giving indications, cautions, etc., write

REFER TO PDR Page 821

WYNN PHARMACAL CORPORATION
Lancaster Ave. at 51st St., Philadelphia, Pa.

*U.S. Patent 2,895,881

also available INJECTABLE QUINAGLUTE

Retrograde pyelography "without serious reactions"[1]

Unlike other retrograde contrast media, which produce a high reaction rate (25-35%),[1] side effects are negligible with Retrografin—a unique agent that combines Renografin with neomycin, bactericidal agent of choice for addition to urographic media.[2] Efficacy and virtual absence of side effects have been amply confirmed in three reports covering a total of 340 patients.[1,3,4]

Clinicians are impressed by the diagnostic quality of films taken after Retrografin; well-defined radiographs, uniformly excellent in detail, have been consistently obtained.[1,3] Retrografin permits retrograde pyelography in patients with a known or suspected active urinary infection. Moreover, with Retrografin, new infection or spread of established infection does not occur.[1,3,4]

Retrografin

Squibb Diatrizoate Methylglucamine Injection U.S.P. with Neomycin Sulfate U.S.P.

Supply: Retrografin is supplied in 25 cc. and 50 cc. vials containing Renografin 30% with 2½% Neomycin as the sulfate. *Also available:* ***Renografin-30*** in vials of 50 cc.

For full information, see your Squibb Product Reference.

'RETROGRAFIN'® AND 'RENOGRAFIN'® ARE SQUIBB TRADEMARKS.

References: (1) Brimberg, J.; Berlowitz, H. D.; Schwinger, H. N.; Renner, M. J.; Lopyan, M.; and Beilouny, R.: New York State J. Med. *59*:2186 (June 1) 1959. (2) Roth, R. B.; Kaminsky, A. F.; and Hess, E.: J. Urol. *74*:563 (Oct.) 1955. (3) Bloom, J., and Richardson, J. F.: J. Urol. *81*:332 (Feb.) 1959. (4) Samellas, W.; Biel, L., Jr.; and Draper, J. W.: New York State J. Med. *59*:2570 (July 1) 1959.

SQUIBB *Squibb Quality—the Priceless Ingredient*

SQUIBB DIVISION Olin M.W.

ANNALS OF
INTERNAL MEDICINE

Volume 55 December 1961 Number 6

Peptic Ulcer in Primary Hyperparathyroidism

An Analysis of Fifty-two Cases

W. T. WILDER, M.D., BOY FRAME, M.D., F.A.C.P., and W. S. HAUBRICH, M.D.
Detroit, Michigan

RECENT MEDICAL EXPERIENCE suggests that an awareness of the association between peptic ulcer and hyperparathyroidism may increase the yield of early diagnosis in primary hyperparathyroidism. This paper analyzes the clinical relationships in 52 patients who had both hyperparathyroidism and peptic ulcer.

Fourteen cases of parathyroid adenoma were proven at Henry Ford Hospital between 1934 and 1957, and in none of these was there a history of peptic ulcer. On the other hand, between 1958 and 1960, seven of ten proven cases of hyperparathyroidism exhibited peptic ulcer either before or at the time parathyroid hyperfunction was diagnosed (Table 1). Four of these cases were uncovered during an 18-month survey of 300 consecutive cases of peptic ulcer (1).

Early reports of Boyd, Milgram, and Stearns (2), and Pemberton and Geddie (3) mentioned digestive complaints in patients with hyperparathyroidism. Gutman, Swenson, and Parsons (4) were the first to stress gastrointestinal symptoms, but it was not until 1946 that Rogers (5) first postulated a relationship between peptic ulcer and hyperparathyroidism. Many recent studies permit a more meaningful interpretation of this association. Hellström's review (6) of this subject in 1959 is particularly noteworthy.

Received June 5, 1961; accepted for publication July 25, 1961.

From the Divisions of General Medicine and Gastroenterology, Henry Ford Hospital, Detroit 2, Michigan.

Presented at the Forty-second Annual Session of The American College of Physicians, Miami Beach, Florida, May 8–12, 1961.

Requests for reprints should be addressed to Boy Frame, M.D., Henry Ford Hospital, Detroit 2, Mich.

CASE MATERIAL AND METHODS

Fifty-two cases of hyperparathyroidism associated with peptic ulcer were analyzed. Seven were patients studied at the Henry Ford Hospital, and 45 were chosen for the most part from recently published reports selected on the basis of adequate data (5–29). In reviewing the material for this study, the following factors were determined in each instance: (a) the pa-

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TABLE 1. Incidence of Peptic Ulcer in Cases of Hyperparathyroidism

Year	Hyperparathyroidism	Ulcer
1934–1957	14	0
1958–1960	10	7

tient's age and sex; (b) the anatomical site of peptic ulceration as confirmed by radiologic examination at any time during the course of the disease; (c) the estimated duration of the ulcer diathesis before parathyroid surgery was performed (determined by the earliest radiologic demonstration of ulceration or, lacking this, by the onset of typical ulcer pain; (d) the state of ulcer activity at the time of parathyroid surgery (assessed on the basis of either the radiologic demonstration of the ulcer, or the presence of typical ulcer pain); (e) the course of ulcer disease prior to and following surgical treatment of the hyperparathyroidism; and (f) the pathologic findings at surgery or autopsy.

The small number of cases and the lack of complete information in many instances permit only impressions and not statistical analysis.

RESULTS

AGE

Twenty-six of the 52 cases were in the fourth decade at the time hyperparathyroidism was diagnosed (Table 2). This coincides with the greatest age frequency reported both for peptic ulcer in the general population (average 30 to 60 years), and for hyperparathyroidism without ulcer disease (average 40 to 50 years). The age range was from 10 to 67 years.

TABLE 2. Age at Time of Diagnosis of Hyperparathyroidism

Years	Number of Cases
10–20	1
20–30	2
30–40	6
40–50	26
50–60	6
60+	4
Unknown	7
Total	52

TABLE 3. Sex Incidence in Surveyed Cases

Sex	Number of Cases
Male	31
Female	17
Unknown	4
Total	52

SEX

Of the 52 cases studied, 31 were male, 17 were female, and sex was not listed for four (Table 3).

SITE OF ULCER

Gastric ulcers were diagnosed in nine patients, compared with 41 instances of duodenal ulcer (Table 4). In two cases both gastric and duodenal ulcerations were present. Other sites of peptic ulceration were esophagus (one case), gastrojejunal stoma (one case), and jejunum (three cases). Of the three cases in which a jejunal ulcer was noted, one patient also had gastric and duodenal ulcers, and subsequently was found to have islet cell hyperplasia and pancreatic adenomas (28). Another, having refused parathyroid surgery, died of a perforated jejunal ulcer (26). Pancreatic disease was not mentioned in the autopsy study in this instance nor in the third patient (7) with jejunal ulcer who died before a definitive diagnosis was made.

DURATION OF ULCER DISEASE BEFORE DIAGNOSIS OF HYPERPARATHYROIDISM

The majority of the patients, 23, had ulcer symptoms for ten to 20 years (Table 5). On the other hand, most of the 16 cases

TABLE 4. Site of Ulcer

Gastric	9
Duodenal	41
Combined	2
Total	52

TABLE 5. Duration of Ulcer before Parathyroid Surgery

Years	Number of Cases
Under 5	16
5–10	9
10–20	23
20–30	2
30+	1
Undetermined	1
Total	52

in which ulcer duration was less than five years have been reported after 1950, since there has been an increased interest in the associated diseases.

ACTIVITY OF ULCER AT THE TIME OF PARATHYROID SURGERY

Twenty-six of the 52 cases were active, and 13 were inactive (Table 6). In the remainder it was impossible to judge the activity from available information.

COURSE OF THE ULCER DISEASE

The term "intractable" was arbitrarily chosen to indicate patients who presented a history of either recurrent or progressive ulcer disease (Table 7). This was determined by evidence of a radiologically persistent lesion or by recurrent ulcer symptoms. Accordingly, 35 of 52 cases were classified "intractable" before parathyroid surgery.

A single episode of peptic ulcer without recurrent symptoms was reported in 15 of 52 cases. For present purposes these latter were classed as "benign."

TABLE 6. Activity at Time of Parathyroid Surgery

State of Ulcer	Number of Cases
Active	26
Inactive	13
Unknown	13
Total	52

TABLE 7. Course of Ulcer Disease before Parathyroid Surgery

	Number of Cases
Intractable	35
Benign	15
Unknown	2
Total	52

COURSE OF ULCER DISEASE AFTER PARATHYROID SURGERY

Twenty-eight patients had either an intractable preoperative course or had evidence of ulcer activity at the time of parathyroid surgery (Table 8).

It was found that the ulcer symptoms of 23 patients in the above category undergoing parathyroid surgery were improved after the operation. Of the three patients who were unimproved following parathyroid surgery, one was later found to have islet cell hyperplasia and pancreatic adenomas, with relief of gastrointestinal symptoms following subtotal pancreatectomy (28). Further long-term follow-up will be necessary to evaluate accurately the course of the ulcer disease following surgical correction of the hyperparathyroidism.

PATHOLOGY

In the 52 patients, 36 showed a single adenoma, and 12 exhibited parathyroid hyperplasia (Table 9). In one case both

TABLE 8. Effect of Parathyroid Surgery on Course of Ulcer Disease

	Number of Cases
Improved	23
Unimproved	3
Unknown	2
Total	28*

* Twenty-eight cases had operations with intractable preoperative course or ulcer activity, or with both, at the time of operation.

TABLE 9. Pathology

Adenoma	36
Hyperplasia	12
Adenoma and hyperplasia	1
Carcinoma	1
Unknown	2
Total	52

adenoma and hyperplasia were described simultaneously (17). One subject had parathyroid carcinoma (18), and in two others (12, 26), the diagnosis was made on biochemical evidence alone without pathologic confirmation. In two cases (19, 20), a mediastinal parathyroid adenoma was found. When hyperplasia was demonstrated it was usually of the clear cell type. However, the number of reports specifying the predominant cell type is insufficient for analysis.

Discussion

From the data presented, certain pertinent features of the association between peptic ulcer and hyperparathyroidism should be amplified. In addition, the clinical and experimental evidence bearing upon this relationship will be reviewed.

There was no significant difference in age among cases of uncomplicated ulcer, hyperparathyroidism with ulcer, and hyperparathyroidism without ulcer. The present series indicates that the male to female ratio approximated 2 : 1, while in ordinary duodenal ulcer disease this ratio is 4 : 1 (30). These findings suggest a relatively increased incidence in females when ulcer is associated with hyperparathyroidism, which is in keeping with the increased incidence of hyperparathyroidism in females (31, 32). The occurrence of duodenal to gastric ulceration approached a 4 : 1 ratio in this series. This is less than the usual incidence of duodenal to gastric ulcers in the general population which ranges between 8 and 12 : 1 (30), and would suggest a relatively greater occurrence of gastric ulcer in hyperparathyroidism.

In 23 of 37 cases the ulcer history antedated the renal or skeletal signs of hyperparathyroidism. In these cases it is possible that appropriate study early in the ulcer phase might have resulted in earlier diagnosis of the underlying endocrine disorder. In two instances from the literature (14, 18), and in three of our cases, symptoms of peptic ulcer were the only clue to the diagnosis of hyperparathyroidism.

One-half of the patients in the series showed ulcer activity at the time of parathyroid surgery. However, one-quarter of the patients who had past histories of peptic ulcer failed to show ulcer activity when overt hyperparathyroidism was diagnosed. If increased parathormone levels, or hypercalcemia, or both, play a role in the production of gastroduodenal ulcer in its association with hyperparathyroidism, it is difficult to explain the lack of ulcer activity in one-quarter of the patients at the time of surgical intervention for parathyroid adenoma.

The majority of the patients with the associated diseases demonstrated a more chronic and episodic course of ulcer disease than usual. This is of practical importance when a patient with peptic ulcer disease is recommended for gastric surgery. Some authors (33) are of the opinion that routine screening of patients for hyperparathyroidism before gastric surgery is mandatory.

In many of the "intractable" ulcer cases in this study, the presence of persistent vomiting without evidence of actual pyloric obstruction was a prominent feature. This was particularly noted in patients who developed hypercalcemic crises. Some of this group experienced aggravation of their ulcer symptoms on the milk-alkali diet, a fact often stressed in the literature. Mild heartburn and nondescript "indigestion" after meals, without the classic history for peptic ulcer or X-ray confirmation, may on occasion have significance in diagnosing the underlying endocrine disorder.

In this series 23 of 28 patients, on whom

sufficient follow-up information was available, were relieved of peptic ulcer symptoms after parathyroid surgery, and improvement was usually prompt. This suggests a more than coincidental relationship between the two diseases, although one must consider the propensity for spontaneous remission and exacerbation of peptic ulcer. If peptic ulcer disease recurs after parathyroidectomy, the possibility of recurrent hyperparathyroidism or other endocrine adenomas must be kept in mind. Because the period of follow-up in the majority of the cases reviewed has been five years or less, future long-term studies are needed to determine the true course of peptic ulcer disease following parathyroid surgery.

The finding that parathyroid adenoma occurred only three times more often than hyperplasia in the present series indicates a relatively increased frequency of hyperplasia. Ordinarily, parathyroid adenoma is ten times more frequently found as a cause of hyperparathyroidism (22). The difficulty often encountered in distinguishing parathyroid hyperplasia from adenoma is well known. A recent report by Cope, Keynes, Roth, and Castleman (22) described the condition of primary chief-cell hyperplasia in association with a high incidence of peptic ulcer and other endocrine adenomas. Increased interest recently has been shown in the syndrome of adenomas occurring in multiple endocrine organs. In this condition there is a striking familial association and a 30% coincidence of peptic ulcer (34). It has been suggested that the tendency toward multiple endocrine adenomas and toward peptic ulcer may be separate hereditary features (35), but an endocrine basis for the ulcer diathesis is still an excellent possibility even if unproved as yet.

The simultaneous occurrence of two separate diseases, such as peptic ulcer and hyperparathyroidism, is of interest for several reasons. The presence of the two diseases may be only coincidental, or there may be an etiologic relationship; that is, one of the diseases predisposes to or brings about the second disease. On the other hand, the two diseases may be inherited together without a cause and effect relationship. The simultaneous occurrence is also of importance when the diagnosis of one is masked by the presence of the second, or when there are similar presenting signs and symptoms. Finally, the concurrence of the two diseases may present problems in treatment, in that therapy for one disease may aggravate or mask the second.

Of prime importance is the consideration of an etiologic relationship between peptic ulcer and hyperparathyroidism. There is no proof that peptic ulcer predisposes one to the development of hyperparathyroidism, even though peptic ulcer often precedes the hyperparathyroidism by years, and before other manifestations of the latter appear. Diets high in calcium and phosphorus used in the treatment of peptic ulcer do not, as far as is known, lead to parathyroid hyperfunction. The only generally accepted stimulus for parathyroid in man is hypocalcemia. If peptic ulcer or its treatment did lead to hyperparathyroidism, the common occurrence of peptic ulcer disease would be expected to lead to a greater incidence of hyperparathyroidism than is found. Therefore, the evidence is interpreted to indicate that peptic ulcer or its treatment does not predispose one to hyperparathyroidism.

There is no facile answer to the question of whether hyperparathyroidism predisposes one to peptic ulcer. The incidence of peptic ulcer in several of the reported series of hyperparathyroidism has been described as 8.8, 11.5, 17.5, and 25% (6, 18, 36, 37). An accurate estimate cannot be made, but we interpret the data to suggest that the frequency of peptic ulcer in hyperparathyroidism exceeds the generally accepted 5 to 10% incidence of peptic ulcer in the general population (6, 30). Ostrow, Blanshard, and Gray (38) have recently reported a re-

view of several large series of hyperparathyroidism and ulcer, and concluded that there was not an increased incidence of peptic ulcer in hyperparathyroidism. It is pertinent to point out that their results were based upon cases studied mainly in the years before there was an increased awareness of the association of these diseases, and this may account for the apparent discrepancy.

There are several possible explanations for the association of the two diseases: (a) a factor implicit in the parathyroid hormone itself, and (b) a secondary influence by the hypercalcemia induced by excessive parathormone. In turn, the injurious factor can exert its ulcerogenic effect by: (a) stimulating acid peptic secretion by the stomach and injuring the gastrointestinal mucosa directly, or (b) by inhibiting the inherent tissue resistance to acid peptic digestion. Neither clinical experience nor laboratory investigation has as yet defined these factors. Efforts in this direction are hampered because the precise etiology of ordinary peptic ulcer disease remains an enigma.

Laboratory experiments pertaining to the influence of parathyroid hormone on gastric function yield conflicting data. Among the earlier workers, Keeton (39) reported that parathyroidectomy in cats lowered the volume, acidity, and pepsin content of gastric secretions; these values were restored by the administration of calcium. Lebedinskaia (40), working with dogs, later indicated that partial resection of the parathyroids depressed the neural phase, but enhanced the chemical phase of gastric secretions. Babkin, Komarov, and Komarov (41) found the administration of parathormone to dogs depressed gastric secretions; this inhibitory effect was predominantly on the neural phase of stimulation. Schiffrin (42) claimed that parathyroid hormone sufficient to elevate the serum calcium also lowered volume and acidity of gastric content in dogs with Pavlov pouches (nerve supply intact), but increased volume and acidity in Heidenhain pouches (nerve supply severed). In the same report thyroid-parathyroidectomy was followed by increased gastric secretions (in both Pavlov and Heidenhain pouches). This increase was inhibited by the administration of calcium lactate or parathormone, but not by thyroid extract. Recently, Donegan and Spiro (43) reported that in human subjects acute infusion of parathormone induced a significant increase in total pepsin and secretory volume. Further, these workers made the pertinent observation that there was no significant change in gastric secretions in five patients before and after the resection of parathyroid adenomas. A similar observation was recorded by Kirsner (44).

Studies relating to the effect of changing calcium ion concentration on gastric secretion are equally confusing. Pravdina (45) found that hypocalcemia was attended by increased gastric acid secretion in dogs. This was confirmed by Schifflers (46). Delrue and Van Damme (47), and later Gray and Adkison (48) observed that an environment either lacking or overly rich in calcium inhibited elaboration of hydrochloric acid from isolated frog gastric mucosa. Grant (49) observed that infusion of calcium salts inhibited both neural and hormonal mechanisms. Lastly, and in contrast, Donegan and Spiro (43) demonstrated that the infusion of calcium gluconate induced increased volume, lower pH, and increased pepsin secretion, but not to those levels seen after histamine. It is apparent that the precise relation between parathyroid hormone, calcium concentration, and gastric secretion (if such a relation exists) has not been defined.

Considering the effect of hypercalcemia and excessive parathyroid hormone directly on the gastrointestinal mucosa, there is both clinical and experimental evidence to prove that visible mucosal injury may be induced. These changes have been variably described

and include mucosal hyperemia, edema, petechiae, glandular necrosis, and focal calcification in gastric glands (50). In no experiment was a typical round peptic ulcer induced, but it is conceivable that a more acute injury might serve as a nidus for its later development. Hellström (6) objects to ascribing the ulcer disease to these mucosal changes on the grounds that: (a) the clinical peptic ulcer occurs with chronic hyperparathyroidism, rather than with the acute hyperparathyroid crisis in which acute mucosal abnormalities have been observed; and (b) the peptic ulcers are more commonly situated in the duodenum, whereas the mucosal changes are more widespread in the stomach and small intestine. Although gastric acid peptic secretion may be indispensable to ulcerogenesis, it is by no means the only factor. From the available evidence it would seem that hyperparathyroidism contributes to peptic ulcer disease by means other than enhancing gastric secretions.

The possible hereditary relationships between peptic ulcer and hyperparathyroidism must be considered. Familial association of peptic ulcer and hyperparathyroidism has been reported in several instances (34, 51, 52). We have been impressed by the frequency of a family history for peptic ulcer disease in certain patients with hyperparathyroidism. One such patient has three additional family members who have peptic ulcer, but no biochemical evidence of hyperparathyroidism. Jackson (34) has reported on the occurrence of peptic ulcer in several members of a family in which at least two members had hyperparathyroidism. He suggests that the frequency of peptic ulcer in hyperparathyroidism may be related to some factor in the hyperparathyroid individual which brings out the underlying ulcer tendency. The possibility that the peptic ulcer in such instances is a feature of polyendocrine adenomatosis should be kept in mind.

At this time, the exact relationship between peptic ulcer and hyperparathyroidism cannot be defined. Common hereditary features may well predispose one to the development of the two diseases. Hyperparathyroidism may then be one of the many forces favoring the development of ulcer activity, perhaps through an adverse effect on mucosal protective factors rather than through an increase in gastric secretions.

Summary and Conclusions

A total of 52 cases of hyperparathyroidism associated with peptic ulcer were studied from the literature and from the files of Henry Ford Hospital. Analysis of these cases resulted in the following conclusions:

1. Age difference was not a significant factor among cases of hyperparathyroidism with ulcer, hyperparathyroidism without ulcer, and ulcer unassociated with parathyroid hyperfunction.

2. There appeared to be a relative increased incidence of females presenting with hyperparathyroidism and ulcer.

3. The duodenum was the most frequent site of ulcer in patients with hyperparathyroidism, but there was a somewhat increased incidence of gastric ulcer in the associated diseases.

4. In the majority of the cases, 23, 10 to 20 years elapsed before hyperparathyroidism was diagnosed. In 23 of 37 cases, where adequate data on this point were available, peptic ulcer was the earliest single symptom complex that could be retrospectively attributed to hyperparathyroidism.

5. One-half of the 52 cases showed ulcer activity, and one-quarter had inactive ulcer disease at the time of parathyroid surgery. In the remainder, the status of ulcer activity at the time of surgery could not be determined.

6. Of 28 patients who had a progressive or recurrent ulcer diathesis, or both, all but three showed definite improvement following parathyroid surgery.

7. Pathologic study of surgical or autopsy specimens revealed a predominance of parathyroid adenoma in the series, but an increased incidence of hyperplasia.

8. It has been our experience that recognition of this association has been a useful aid in arriving at the early diagnosis of hyperparathyroidism.

Summario in Interlingua

Le analyse de 52 casos de hyperparathyroidismo associate con ulceres peptic, que esseva colligite ab le litterature e le archivos del Hospital Henry Ford, ha resultate in le sequente conclusiones: (a) Le incidentia de femininas inter le patientes con le duo morbos in association es levemente plus alte que le incidentia de masculos; (b) in 23 del 52 patientes, inter 10 e 20 annos de ulceriferitate passava ante que hyperparathyroidismo esseva diagnosticate. In 23 de 37 casos (in que adequate datos esseva disponibile), ulcere peptic esseva le plus precoce complexo de symptomas que poteva esser attribuite in retrospecto al presentia de hyperparathyroidismo; (c) il ha un relativemente augmentate incidentia de ulceres gastric in casos del morbos in association; (d) le majoritate del patientes experientiava un inusualmente chronic e episodic curso de lor ulcerismo, con melioration de illo post le chirurgia parathyroide; (e) il ha un augmentate incidentia de hyperplasia parathyroide inter le casos in que ulceres es associate con hyperparathyroidismo; e (f) in le experientia del autor, le recognition del presentia de ulcerismo peptic se ha repetitemente provate plus utile in le precoce diagnose de hyperparathyroidismo que le recognition del presentia de calculuos renal. Es presentate un revista de datos laboratorial in re le relation de hormon parathyroide con le concentration de calcium e le secretion gastric. Possibile mechanismos etiologic es discutite.

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The Lente Insulin Triad

With Emphasis on the Use of "Lente Combinations"

FRED W. WHITEHOUSE, M.D., F.A.C.P., WILLIAM L. LOWRIE, M.D., F.A.C.P.,
EARL REDFERN, M.D., and JOHN B. BRYAN, M.D.
Detroit, Michigan

FOR THE LAST FIVE YEARS the medical literature on the therapy of diabetes mellitus has dealt generously with the use of the oral hypoglycemic agents. The indications and limitations of these drugs are now clear. Their use is limited to the patient with maturity-onset diabetes. They are ineffective in the patient with growth-onset diabetes who lacks endogenous insulin. The limited applicability of the oral hypoglycemic agents has re-emphasized the importance of insulin. Insulin, when used correctly, is effective in all patients with diabetes. The proper use of insulin must be mastered by those accepting the responsibility of the care of the diabetic patient.

Currently, the clinician has several insulin preparations from which to choose. Crystalline zinc insulin * is available for control of the diabetic state during periods of acute stress, such as keto-acidosis, surgery, or severe infection. Crystalline zinc insulin may also be used along with a preparation of depot insulin for day-to-day regulation of the diabetes. Protamine zinc insulin enjoyed wide popularity after its introduction in 1937. Its use has declined in recent years. A sluggish onset of hypoglycemic activity plus an excessive nocturnal effect has proved disadvantageous. In the average patient with severe diabetes who used protamine insulin alone, daytime glycosuria existed, yet nocturnal hypoglycemia was common. Initially, this problem was corrected with the use of crystalline zinc insulin and protamine zinc insulin in separate injections each morning. The use of an appropriate mixture of these insulins given once a day followed in natural sequence. The currently popular preparations of intermediate insulin evolved from these early mixtures. While globin insulin is less commonly used, isophane insulin and lente insulin are widely accepted.

In 1952, Hallas-Moller, Jersild, Petersen, and Schlichtkrull (1, 2) reported on two new preparations of insulin. They combined small concentrations of zinc with insulin at the pH of the blood. Insoluble insulin-zinc suspensions resulted. This was accomplished by using acetate as a buffer instead of phosphate. The use of acetate permitted a greater union of zinc with insulin than did the use of the phosphate salt. Two physical fractions, an amorphous precipitate of zinc-insulin, and a solution of zinc-insulin crystals, were obtained through altering the pH of the insulin-zinc suspension. The crystalline fraction simulated protamine zinc insulin in the onset, peak, and duration of its hypoglycemic activity. The physiologic effect of the amorphous fraction proved to be somewhat slower in onset and longer in duration than crystalline zinc insulin, though shorter than isophane insulin. Neither fraction contained

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Requests for reprints should be addressed to Fred W. Whitehouse, M.D., Henry Ford Hospital, Detroit 2, Michigan.

* Regular or amorphous insulin is no longer produced commercially.

added foreign protein. The crystalline (long-acting) fraction was called ultralente, while the amorphous (short-acting) product was named semilente. Neither preparation of insulin alone proved suitable for broad clinical use. Ultralente had all the disadvantages of protamine zinc insulin, and semilente was much too brief in action for a single daily dose to satisfactorily control the blood sugar for a 24-hour period. A suitable combination of ultralente and semilente was devised which minimized these disadvantages. A combination with a ratio of 70% ultralente and 30% semilente permitted 24-hour control of the blood sugar with a single daily injection in the maximal number of insulin-dependent patients. A combination with this ratio of ultralente and semilente was commercially prepared and called lente insulin. Its hypoglycemic activity is almost identical to isophane insulin. Table 1 compares the physiologic characteristics of the three members of the lente family.

Marble (3), Haunz (4), and others (5–7) have recorded their experience with the use of lente insulin alone. Its usefulness clinically is identical to that of isophane insulin. The hypoglycemic activity of lente insulin is somewhat longer in duration than globin insulin. Because of the close similarity to isophane insulin, many found it difficult to predict any practical advantage to lente insulin. The slightly lower incidence of allergic reactions due to the absence of foreign protein (protamine or globin), and the theoretical advantage of freedom from the "anti-heparin" effect of protamine, seemed of little practical significance. Consequently, the application of lente insulin alone was only sporadic until the component parts of lente, ultralente, and semilente became available commercially. With all three preparations available, their combined use provided certain advantages over isophane insulin. Our experience in the last four years with the use of these three preparations prompted the writing of this paper.

TABLE 1. The Hypoglycemic Activity of the Lente Triad

Insulin	Action	Peak*	Duration*
Ultralente	Very slow	18–24	36+
Lente	Slow	8–14	20–26
Semilente	Fast	2–4	10–12

* In hours after injection.

RESULTS

A combination of two of the three members of the lente family was given to 65 patients. These patients have been followed for six to 36 months; 43 for over one year. While the age range of these patients is broad, the majority are now under age 40. Twenty-four patients have had diabetes for more than 15 years. The majority have been controlled with a suitable combination of lente and ultralente. This fact emphasized the occurrence of nocturnal hyperglycemia in the patient with insulin-deficient diabetes. In our experience the failure of a significant 24-hour hypoglycemic effect by an intermediate insulin alone is a common cause of poor control in the diabetic patient dependent on insulin. When greater hypoglycemic activity was desirable during the day, we prescribed semilente and lente. In a few cases a combination of ultralente and semilente was given. Individual examples cited below will expand upon these problems. Table 2 summarizes these data.

Most of these patients were normal in weight. The obese person with diabetes rarely needs a combination of insulin; he needs more rigid dietary control. Our patients requiring a combination of insulin had growth-onset diabetes, were prone to ketosis, and some showed wide fluctuations in the blood sugar. In order to minimize error and emphasize simplicity, combinations of insulin were used only when clearly indicated. Some patients in this group had previously taken different combinations of

TABLE 2. Summary of 65 Patients Treated at Henry Ford Hospital with a "Lente Combination"

Age	5 to 70 years (36 under age 40)	
Sex	29 men and 36 women	
Duration of diabetes	1 to 30 years (24 over 15 years)	
Follow-up	6 to 36 months (43 over 12 months)	
Combination used	Ultralente and lente	42
	Semilente and lente	18
	Semilente and ultralente	5

insulin or multiple daily injections of insulin. Others were unsatisfactorily regulated on a single daily injection of an intermediate insulin alone. The case reports below illustrate a few of the pertinent facts we have learned.

We employ lente insulin alone almost exclusively in the regulation of patients requiring insulin who are undergoing initial control or revision of control of their diabetes.

CASE 1

A Newly Discovered Diabetic in Need of Insulin: The patient was 67 inches tall and weighed 145 pounds. This 39-year-old salesman consulted us because of a ten-pound weight loss, polyuria, and polydipsia. An initial post cibum blood sugar was 502 mg/100 ml. Regulation with a 2,100 calorie diet and lente insulin was accomplished with ease. Table 3 records the clinical data during his original hospitalization and initial follow-up. After he showed a nice remission in severity, insulin was replaced with an oral hypoglycemic agent. Three and one-half years later, because of difficulty in maintaining an ideal weight, lente insulin was reinstituted.

Comment: The majority of adults who require insulin for control of diabetes can be regulated successfully on a single dose of lente insulin before breakfast. There is no need for combinations of insulin in these patients. Isophane insulin is also quite satisfactory and may be interchanged unit for unit with lente insulin. A mid-afternoon feeding will minimize the occurrence of hypoglycemia before supper, and a bedtime snack will stabilize the level of the blood sugar during the night. The fasting blood sugar as well as the post cibum levels generally remain in a satisfactory range once the proper dose of insulin is found. Many children and some adults will not be controlled this easily. However, it is successful often enough to justify an initial trial of regulation with lente insulin alone. We have failed to substitute successfully a single dose of lente insulin alone for a two-dose daily schedule of isophane insulin. The reverse is also true. In a given patient the hypoglycemic activity of isophane and lente insulin is identical.

When a patient has been taking intermediate insulin once a day, and there is daytime hyperglycemia and glycosuria in spite of fasting normoglycemia, the situation calls for consideration of a "lente combination."

CASE 2

More Hypoglycemic Activity during the Day is Needed: The patient was 67 inches tall and weighed 145 pounds. This 39-year-old postman was first seen one year after onset of diabetes. His complaints were inability to gain weight, and fatigue. Urine testings for glucose at home were constantly positive. He was following a 2,400 calorie diet and taking 90 units of isophane insulin once a day. His weight at the first visit was 130 pounds. Initially, a random blood sugar was 235 mg/100 ml. Physical examination was normal except for evidence of underweight. Control of his diabetes was established with the use of a quantitative diabetic diet, an increase in the total daily dose of insulin, and an adjustment of the time-action of the insulin. Table 4

TABLE 3. The Use of Lente Insulin Alone

Case 1	Diet (grams): Carbohydrate, 200; Protein, 100; Fat, 100.				
	Insulin*			Blood Sugar†	
Day	8 AM	12 PM	5 PM	Fasting	3 PM
1	0	0	0		502
2	20L	0	6C		197
3	26L	6C	6C	160	180
4	30L	0	6L		144
5	36L	0	0	100	
6	36L	0	0	124	
7	36L	0	0	78	
	Diet (grams) to: Carbohydrate, 220; Protein, 120; Fat, 120.				
10	26L	0	0		139
31	12L	0	0		100

* L = Lente; C = Crystalline zinc insulin.
† In mg/100 ml.

TABLE 4. The Combination of Semilente and Lente

Case 2	Diet (grams): Carbohydrate, 160; Protein, 100; Fat, 100.					
	Insulin*			Blood Sugar†		Urine
Day	8 AM	12 PM	5 PM	Fasting	3 PM	Sugar‡
1	90N	20C	20C	151	260	
2	90L	10C	20C		364	
3	100L	15C	20C	80	288	50
4	100L+20SL			150	—	43
5	100L+50SL			180	280	29
6	100L+50SL			55	230	29
7	120L+50SL			95		15
13	120L+50SL			60		6
	Diet (grams) to: Carbohydrate, 200; Protein, 140; Fat, 140.					
23	120L+50SL				138	
47	100L+40SL				85	
64	80L+30SL			100		

* N = Isophane; C = Crystalline zinc; L = Lente; SL = Semilente.
† In mg/100 ml.
‡ In grams per 24 hours.

charts the regulation of the diabetes of this patient. At first, with lente insulin alone, there was fasting normoglycemia, yet persistent hyperglycemia and glycosuria during the day. This was corrected with the use of a combination of lente and semilente insulin. His weight at discharge was 133 pounds. Ten days later, his weight was 139 pounds and two months later, his weight was stable at 152 pounds. Since then his weight has been maintained at this level and his daily requirement of insulin has stabilized at 110 to 120 units given as a combination of semilente and lente.

Comment: In our experience, the use of semilente and lente insulin in combination is less frequent than the use of ultralente and lente. The former combination is indicated when, with the use of lente insulin alone, fasting normoglycemia exists, yet daytime hyperglycemia and glycosuria persist. Nocturnal hypoglycemia may also be an indication, though this is much less common with an intermediate insulin than with the use of protamine zinc insulin. When a faster-acting insulin is needed, there seems to be little choice between the use of crystalline zinc insulin and semilente insulin in a combination with lente insulin. This case and others lead us to believe that a significant preference for one is rare. Our interest in combinations of the lente triad has prompted us to use the combination of lente and semilente more frequently than the mixtures of lente and crystalline zinc insulin.

A more common problem requiring the "tailoring" of the hypoglycemic activity of the insulin prescription is exemplified by the next case.

CASE 3

Two Episodes of Keto-acidosis within a Month: The patient was 68 inches tall and weighed 160 pounds. This 46-year-old salesman had had diabetes for 14 years. He was first seen in 1957 for a general medical evaluation. Physical examination then was normal, except for a grade II diabetic retinopathy (microaneurysms). His insulin prescription was 55 units of isophane insulin once a day. An initial fasting blood glucose was 252 mg/100 ml, while two levels of blood glucose measured before lunch were 70 and 150 mg/100 ml, respectively. He was not seen again until May 1959. At this time he was admitted to the emergency room in mild diabetic keto-acidosis. This was easily corrected with fluids and 120 units of crystalline zinc insulin. Control was established again with an 1,800 calorie diabetic diet and 48 units of lente insulin alone. Table 5a records his first hospitalization. One month after discharge, he was re-admitted for treatment of mild diabetic keto-acidosis. Intravenous fluids and 100 units of crystalline zinc insulin once again corrected the metabolic imbalance. Table 5b records the data during and following this admission. At this time a combination of lente and ultralente insulin was prescribed. After initial adjustments in his daily dose of insulin, a stable combination of lente and ultralente was found which has been continued to the present. No further keto-acidosis has occurred.

Comment: The second episode of keto-acidosis could have been avoided. Fasting hyperglycemia at the time of the initial examination in 1957 suggested a failure of the 24-hour hypoglycemic activity of isophane insulin. Further examinations at that time were not possible. In May 1959 fasting hyperglycemia during the first hospitalization was apparent (Table 5a). A small amount of lente insulin given on the evening of the fifth hospital day resulted in fasting normoglycemia the next morning. The first fasting blood glucose after discharge was elevated. The use of ultralente in combination with lente resulted in more satisfactory levels of blood glucose (Table 5b). The patient gained ten pounds. His total daily dose of insulin is

TABLE 5a. The Combination of Ultralente and Lente

Case 3	Diet (grams): Carbohydrate, 180; Protein, 90; Fat, 90.				
	Insulin*			Blood Sugar†	
Day	8 AM	12 PM	5 PM	Fasting	3 PM
1	48L	0	0		225
2	48L	6C	6C	165	
3	48L	8C	0	80	
4	48L	8C	0	330	
5	48L	8C	6L	360	
6	48L	0	0	75	
11	48L	0	0	150	

TABLE 5b. After the Second Episode of Ketosis

1	40L+12UL	240	
2	40L+12UL	270	
3	40L+12UL	90	185
4	44L+10UL	115	
	Diet (grams) to: Carbohydrate, 220; Protein, 130; Fat, 130.		
17	60L+20UL	40	
30	56L+18UL	55	
4 months	54L+18UL	70	
13 months	42L+14UL	115	
19 months	40L+14UL	109	

*L = Lente; UL = Ultralente; C = Crystalline zinc.

† In mg/100 ml.

almost the same as it was in 1957, but now the fasting blood glucose levels are normal.

The diabetic patient who is dependent upon insulin for life is vulnerable to ketosis and acidosis. To assure good control of the diabetes over the 24-hour period, the proper total dose of insulin must be ascertained, as well as the correct timing of the hypoglycemic activity of the insulin. This patient was not protected from metabolic deterioration by lente insulin alone. Proper timing of the hypoglycemic activity through the use of a combination of lente and ultralente insulin corrected this error. The use of lente and ultralente insulin in combination also is indicated when frequent daytime hypoglycemia occurs with lente alone. Many times the use of an intermediate insulin alone will result in too much hypoglycemic activity during the day. If the total daily dose of insulin is then decreased in order to prevent this hypoglycemia, a failure of 24-hour activity of the insulin may subsequently manifest itself as fasting hyperglycemia. In this type of patient, proper timing of the insulin may also be accomplished by the use of two injections daily of either isophane or lente insulin given about 12 hours apart. When two injections of isophane or lente insulin are used, generally 60 to 80% of the total daily dose is given in the morning injection. However, only with the use of lente and ultralente in combination is control established with a single daily injection of insulin. We attempt to simplify the therapeutic program for the patient whenever possible. One daily injection of insulin is easier than two.

CASE 4

The Need for Combinations May Be Temporary: The patient was 67 inches tall and weighed 135 pounds. This 37-year-old man had diabetes for 18 years prior to admission for the treatment of bilateral, advanced, and active pulmonary tuberculosis. Prior to hospitalization, he took 46 units of isophane insulin daily, and followed a 2,100 calorie diabetic diet. Physical examination showed grade III diabetic retinopathy (microaneurysms, hemorrhages, and exudates) and the expected pulmonary findings. The aforementioned regimen for control of his diabetes was continued, although the daily dose of insulin was increased to 56 units because of fasting hyperglycemia. The patient then developed hypoglycemia in the late afternoon, yet fasting hyperglycemia persisted. A combination of 50 units of lente and 10 units of ultralente insulin each morning corrected this problem. This prescription was stable throughout most of his nine-month stay in the hospital. When increasing physical activity was permitted, his daily requirement of insulin decreased. Concomitantly the ultralente insulin proved to be unnecessary. The patient was taking 50 units of lente insulin alone at the time of discharge.

Comment: With physical inactivity and associated stress, some patients will deviate from their usual requirements of insulin. An alteration in the time-action of the insulin may be necessary. This patient exemplifies the need for an increase in the long-acting component of the prescription. Others may need an increase in the short-acting component, at which time either semilente or crystalline zinc insulin may be combined with lente insulin. When the stress passes, satisfactory control with a single injection of lente insulin (or isophane insulin) alone again may suffice. We have noted similar occurrences following surgical stress and acute

infection, and during pregnancy. This type of patient must be followed carefully in the period of recovery in order to avoid hypoglycemia.

Sometimes we advise a change from a mixture of crystalline zinc insulin and protamine zinc insulin to a combination of two members of the lente triad.

CASE 5

Some Mixtures of Insulin Are Better than Others: The patient was 68 inches tall and weighed 125 pounds. Diabetes was diagnosed in this 21-year-old student at age 16. Initial regulation was accomplished with a mixture of crystalline zinc insulin and protamine zinc insulin in a ratio of 2 : 1. Later, lente insulin alone was used in an attempt to avoid the mixing of insulin. This proved to be unsatisfactory, and the prescription was changed to a combination of semilente and ultralente. Table 6 summarizes the progress of this patient during the past three years. The ratio of ultralente to semilente in the combination is altered under the guidance of the fasting blood sugar level and the 24-hour urinary excretion of glucose. The current ratio of ultralente to semilente insulin is very close to that ratio present in lente insulin.

Comment: There is no difference in physiologic action between a combination of 40 units of lente and 20 units of ultralente on the one hand, and a combination of 48 units of ultralente and 12 units of semilente on the other hand. Recall that lente insulin is a combination containing 30% semilente and 70% ultralente.

TABLE 6. The Use of Ultralente and Semilente in Combination

Case 5	Diet (grams): Carbohydrate, 220; Protein, 120; Fat, 120.		
Date	Insulin*	Blood Sugar†	Urine Sugar‡
6–58	36UL+20SL	105	6
10–58	40UL+16SL	130	—
12–58	48UL+12SL	100	21
6–59	44UL+16SL	155	—
5–60	46UL+18SL	65	0
7–60	42UL+22SL	125	15
8–60	46UL+18SL	—	Trace
1–61	42UL+20SL	225	—
7–61	48UL+18SL	125	0

* UL = Ultralente; SL = Semilente.
† In mg/100 ml, fasting.
‡ In grams per 24 hours.

We have no objection to a combination of ultralente and semilente. We employ it infrequently because of convenience and habit. Generally, we initiate therapy with lente insulin alone. If a "lente combination" is needed, we either substitute or add a certain amount of semilente or ultralente insulin to a basic dose of lente insulin. To us, this is more convenient than a change to a combination of ultralente and semilente. Either course is satisfactory. The important point is to identify the patient in need of a combination.

In our opinion, the use of a "lente combination" is preferable to the older mixtures of crystalline zinc insulin and protamine zinc insulin. When the former is used, the physician knows the exact amount of each preparation of insulin in the combination. Each component maintains its autonomy. This is untrue with the mixtures of protamine zinc insulin and crystalline zinc insulin. Here, a given amount of crystalline zinc insulin reacts with the excess protamine present in protamine zinc insulin. This binding of insulin and protamine converts some of the crystalline zinc insulin into protamine zinc insulin. When the mixing of protamine zinc insulin and crystalline zinc insulin is carried out daily in the syringe, variations in the degree of conversion may occur from day to day. Prior mixing of these preparations of insulin in a large vial eliminates the day-to-day variation. While the use of these mixtures was a step toward more adequate control of diabetes, the use of combinations of the lente triad is now to be preferred. Unless there is opposition by the patient, or another compelling reason, we are inclined to change all patients on mixtures of protamine zinc insulin and crystalline zinc insulin to either lente insulin alone or to a "lente combination." As a corollary to this last point, "there is no success like success." It is better for the physician to leave the prescription of a patient undisturbed when (a) control has proven to be satisfactory, or (b) the patient is resistant to change. In the first instance, significant improvement may not be possible. Changing the prescription of insulin in the face of resistance by the patient is fruitless. Some diabetics become very attached to their individual regimen. Rule one is occasionally violated in an attempt to simplify the therapeutic program for the patient.

A few of our patients who previously had taken a mixture of crystalline zinc insulin and isophane insulin once a day have been more satisfactorily controlled with a combination of lente and ultralente.

CASE 6

Intermediate and Long-acting Insulin for Intermediate and Short-acting Insulin: The patient was 65 inches tall and weighed 115 pounds. This 38-year-old executive has had diabetes for 15 years. At her first visit, she was taking a mixture of crystalline zinc insulin and isophane insulin each morning. This program was continued. During a hospitalization for treatment of subacute thyroiditis, persistent fasting hyperglycemia was noted. We changed her prescription to a combination of lente and ultralente. Table 7 shows the results. The daily dose of insulin now ranges between 48 and 56 units.

Comment: At first glance, semilente and lente would seem to be the appropriate combination to use in place of a mixture of isophane and crystalline zinc insulin. Early in our experience this combination was employed in similar patients. Control was unsatisfactory due to afternoon hypoglycemia and fasting hyperglycemia. The use of a combination of lente and ultralente corrected these abnormalities. Six patients have been improved with a combination of lente and ultralente when previously a mixture of isophane and crystalline zinc insulin had been employed. We attribute this to an increase in the nocturnal hypoglycemic activity of the new combination, which results more often in fasting normoglycemia. The hypoglycemic activity of isophane insulin 24 hours after injection must be minimal in this type of patient. The use of extra ultralente insulin prevents rapidly rising levels of blood glucose at breakfast time, thus eliminating the need for a correcting dose of fast-acting insulin. It can be properly argued that the former combination of isophane insulin with crystalline zinc insulin was incorrect.

TABLE 7. The Use of Ultralente and Lente in Place of Isophane and Crystalline Zinc Insulin

Case 6	Diet (grams): Carbohydrate, 180; Protein, 100; Fat, 100.			
	Insulin*	Blood Sugar†		Urine
Day	8 AM	Fasting	3 PM	Sugar‡
1	48N+12C	155	75	23
5	54N+16C	150		
7	54N+12C	270		
8	54N+12C	390	35	48
9	58N+12C	400		
10	56L+12UL	375	170	6
11	56L+12UL	155		13
12	56L+12UL	85		1
13	56L+12UL	115		5
21	48L+10UL	75		
30	44L+12UL	65		

* N = Isophane; C = Crystalline zinc insulin; L = Lente; UL = Ultralente.
† In mg/100 ml.
‡ In grams per 24 hours.

DISCUSSION

The cases cited above exemplify some of the problems raised during the control of the patient with diabetes. The correct use of insulin is imperative for the assurance of good health of the diabetic patient who needs insulin. When diabetes begins during adulthood, satisfactory control can generally be accomplished with a single daily dose of an intermediate insulin. We prefer lente insulin in this situation because: (a) there is no added foreign protein; (b) if an adjustment of the time-action of the insulin is necessary, the ratio of slow to fast-acting insulin, using the lente family, can be altered without abandoning the single daily injection; (c) the regular use of a single type of insulin strengthens the confidence of the physician in its use. The physician should become proficient in the use of a minimal number of suitable preparations of insulin. Skill with a few preparations of insulin is preferred to inexperience in the use of all available preparations.

With the exception of the rare patient with chronic insulin resistance, all situations requiring insulin can be handled by the use of crystalline zinc insulin or the lente triad. As mentioned before, we believe the former should be used during periods of acute stress. When insulin for maintenance therapy is indicated, we begin with lente insulin alone. The use of combinations of lente with semilente or ultralente is then reserved for those specific patients exhibiting the proper indications. Table 8 lists those indications with the assumption that the patient in question is taking an intermediate insulin daily. A few points are worthy of emphasis. The use of ultralente and lente in combination is more

TABLE 8. Indications for the Use of Combinations of the Lente Triad

A. With patient on intermediate insulin, if
1. fasting hyperglycemia or
2. mid-afternoon hypoglycemia,
3. or both;
or
With patient taking more than one injection daily, try *lente and ultralente.*
B. With patient on intermediate insulin, if
1. fasting normoglycemia and
2. daytime hyperglycemia,
try *lente and semilente.*
C. If there is a personal preference, use *ultralente and semilente,* instead of A or B.

common than the use of semilente and lente. It may take weeks or months to determine the final satisfactory combination. Sufficient time should be spent to establish the correct combination, for the patient with diabetes may have an entire lifetime of dependence upon it. The final combination is not rigid, of course, but may be changed from time to time depending upon the circumstances and need. The regular examination of the blood sugar aids in estimating the degree of control. Blood specimens for sugar should be obtained not only in the fasting state, but also at random during the day. The estimation of the urinary loss of glucose in 24 hours is also a helpful criterion of control. Ideally, the urine should be free of glucose; practically, the loss of glucose should be kept below 5% of the daily carbohydrate intake. The physician should remember to make necessary changes in diet in selected cases. Occasionally, the use of a combination of insulin may be avoided by an adjustment of the intake of food. This method should not be carried to an extreme. We believe that an occasional patient cannot be controlled with a single daily injection of any kind or combination of insulin. Even two injections per day may be unsatisfactory. It is reasonable to simplify the regimen for control whenever possible, but it is important to put sound medical advice before convenience. We rarely hesitate to abandon the use of a "lente combination" when it fails to accomplish its intended purpose. While we have very few patients on multiple doses of crystalline zinc insulin daily, we have found that a few children are better off with an injection of intermediate insulin twice daily. A small amount of crystalline zinc insulin is often combined with the morning dose of intermediate insulin. In this situation, we use crystalline zinc insulin with lente (or isophane) in the morning, and lente (or isophane) alone in the evening. Marked lability in the unusual patient may force the use of multiple injections of crystalline zinc insulin daily as outlined by Wildberger and Ricketts (8).

The disadvantages of the lente triad are minor. A hypersensitive patient may complain of burning upon injection of the insulin. We have seen three such cases. The patient must be careful to measure the correct dose of each insulin. Confusion with the final combination of insulin has occurred very infrequently to our knowledge. Allergy to insulin has been absent in these patients. In some of our patients taking a combination of ultralente and lente, we have for several months substituted a program of two injections daily of lente insulin alone. We have failed to identify any patient in whom a striking difference existed between the two parallel programs. In individual cases a preference may exist, especially if lability is marked. Some of our patients take two injections of lente insulin daily, rather than a single injection of lente combined with ultralente insulin, merely to eliminate the chance of error. However, most patients can be successfully instructed in the technique of combining preparations of insulin.

The availability of the triad of lente, ultralente, and semilente insulin has permitted a distinct advance in the use of insulin. Certain advantages over older preparations of depot insulin exist. Further

improvement in the preparation of insulin probably will await the development of an insulin whose absorption and action will depend upon changes in the level of the blood glucose. We feel that protamine zinc insulin has served its useful purpose and is now obsolete. It is wise to keep the number of available preparations of insulin at a minimum.

Summary

A combination of two of the three members of the lente insulin triad was given to 65 diabetic patients who were dependent on insulin. Forty-two received a combination of lente and ultralente; 18 received semilente and lente; five received ultralente and semilente. These combinations were given to patients whose diabetes was uncontrolled with a single daily injection of an intermediate insulin. When greater hypoglycemic activity during the night was desirable, ultralente was combined with lente insulin. Frequently, this permitted the elimination of an evening injection of intermediate insulin. Semilente was used with lente when greater hypoglycemic activity during the day was needed. In our opinion, the use of the lente triad gave satisfactory control of the diabetes in this group of patients. Disadvantages were minor. The use of the lente triad for control of the patient with diabetes dependent on insulin is recommended. Those preparations of insulin containing added foreign protein are outdated. Illustrative cases are recorded.

Summario in Interlingua

Un combination de duo del tres membros del triade de insulina lente esseva administrate a 65 patientes con diabete requirente insulina. Quaranta-duo recipeva un combination de lente e ultralente; 18 de semilente e lente; e cinque ultralente e semilente. Iste combinationes esseva administrate a patientes in qui le diabete non poteva esser stabilisate con un sol injection diurne de un insulina intermediari. Quando un plus forte action hypoglycemic esseva desirate durante le nocte, ultralente esseva combinate con lente. Frequentemente isto permitteva le elimination de un injection vespertin de insulina intermediari. Semilente esseva usate con lente quando un plus forte action hypoglycemic esseva requirite durante le die. In nostre opinion, le uso del triade de lente resultava in un satisfacente stabilisation del diabete in iste gruppo de patientes. Le disavantages esseva minor. Le uso del triade de lente in le stabilisation del patiente con diabete requirente insulina pote esser recommendate. Le preparatos de insulina que contine proteina alien como additivo es antiquate. Casos illustrative es citate.

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Cat-scratch Disease: Complement Fixation and Skin Test Results

S. S. KALTER, PH.D., *Brooks Air Force Base, Texas*

RECENT DESCRIPTIONS of several large patient series emphasize that cat-scratch disease is more prevalent than originally believed (1–4). Since its recognition in 1932 by Foshay, an increasing number of cases have been reported. The syndrome, also called cat-scratch fever, nonbacterial lymphadenitis, or benign inoculation lymphorecticulosis, because of its extreme protean nature, is often confused clinically with other lymphadenopathies.

Most investigators are of the opinion that the disease is of viral etiology. However, such confirmation is lacking, as yet. Mollaret, Reilly, Bastin, and Tournier (5) reported the successful transmission of the disease to humans and monkeys by inoculation of lymph node material from clinical cases. Zwissler, cited by Warwick and Good (6), reproduced the disease in humans, using material from suppurative nodes. Positive skin reactions in patients with cat-scratch disease were obtained by employing as antigen, material passaged in rat testes and chick yolk sacs. More recently, the presence of a "viral hemagglutinin" was described and isolation of an agent suggested (7). Isolation attempts by the majority of investigators have not, however, been successful.

It has been advocated that the inciting agent of cat-scratch disease belongs to the psittacosis-lymphogranuloma venereum group of viruses. Mollaret et al. (5) described the production of inclusion bodies identical with those described for psittacosis. Kalter, Prier, and Prior (3), however, were unable to confirm the occurrence of intracytoplasmic inclusions. Daeschner, Salmon, and Heys (1) refer to feline pneumonitis virus as a possible factor in causation of cat-scratch disease.

Relationship with the psittacosis-lymphogranuloma venereum group of viruses has also been postulated on the basis of the complement fixation test using a group antigen. There is apparent disagreement in results or, more accurately, in interpretation of results, when the complement fixation test is employed. Mollaret et al. (5) found 46.5% of their patients with cat-scratch disease responded with titers of 1 : 10 or higher in the complement fixation test, using lygranum complement fixation (C F antigen) as the test material. The significance of these titers was questioned, however, by Armstrong, Daniels, MacMurray, and Turner (8), even though their data showed a greater percentage of positive reactions among their cases than in control groups.

In a study of cat-scratch disease in New Zealand, Manning and Reid (9) substantiated correlation between positive skin tests for cat-scratch disease and positive complement fixation titers using a lygranum antigen. In a series of 35 patients with positive skin reactions, these investigators found 23% positive response (titers of 1 : 8 or higher). There were no positive complement fixation reactions among 44 patients reacting negatively to skin test for

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Requests for reprints should be addressed to S. S. Kalter, Ph.D., School of Aviation Medicine, USAF Aerospace Medical Center (ATC), Brooks Air Force Base, Texas.

cat-scratch disease; only 2% of 50 control sera, obtained from normal blood donors, showed any evidence of antibody. Spaulding and Hennessy (4) similarly found that 14 of 39 patients (approximately 40%) demonstrated positive complement fixation reactions to the psittacosis-lymphogranuloma venereum group antigen. A control group of 120 persons failed to demonstrate any antibody. Morrissey (10) found seven of ten patients reacting positively to skin test, and two of three persons with negative reactions to skin tests, to have titers of 1 : 32 or greater to the group antigen.

Agreement is more uniform regarding the use of the skin test in diagnosis and its relationship to illness. The skin test seemingly is the most specific test available, although false reactions are infrequently encountered. Unfortunately, the skin test is not without shortcomings. Many individuals continue to react positively for years, possibly throughout life. This persistence of skin reaction introduces a potential error in diagnosis of active disease. For this reason it is advocated that the skin test should not be used diagnostically unless a clearly defined clinical picture exists. Further confusion may result from the great variation to different preparations of antigen for skin testing evidently occurring among patients.

The study presented here was initiated to ascertain the value of the complement fixation test as a laboratory aid in diagnosis of cat-scratch disease. An attempt also was made to evaluate the diagnostic significance of antigens for skin tests by simultaneous testing of a single patient with different preparations of antigen.

Material and Methods

To obtain sufficient material for serologic evaluation of the complement fixation test and for mass skin testing, a contributing program was instituted to supply physicians with antigen for skin tests and, reciprocally, to obtain clinical material. In return for such antigen the following information and material was requested:

1. Age of patient.
2. Extent of adenopathy.
3. Incubation period, that is, time of appearance of adenopathy in relation to association with cats.
4. Occurrence of disease in any other member of the family.
5. Acute and convalescent blood samples.
6. Results of skin test.
7. Suppurative material, if available.

As a result of this program, sufficient antigen was prepared and supplied to test several thousand patients.

The data reported here were accumulated from 130 acute and convalescent serum pairs, representing the same number of patients, and 40 single convalescent sera. A control group of 200 sera from untested individuals, selected to give only comparable age groups, was included. Approximately 75% of the study group was composed of children; the remaining sera were derived from young adults and a few patients of older ages. Since age did not appear to have any direct relationship to the results reported here, no attempt was made to separate the test groups.

Serology: All sera were inactivated at 56 C for one-half hour, and tested in the complement fixation test routinely employed in this laboratory. Following determination of hemolysin and complement units, the optimal dilution of the psittacosis-lymphogranuloma venereum group antigen was determined in a block titration. The method consisted of ascertaining that dilution of antigen showing a 3 or 4+ fixation (that is, inhibition of complement) with the highest dilution of serum. Such dilution was considered to be one unit of antigen. Twofold serum dilutions of acute and convalescent specimens (tested simultaneously) were prepared in veronal buffer (pH 7.4), and 0.1 ml of each dilution was placed in appropriate tubes. Two units antigen in 0.1 ml were added to each serum dilution followed by 2 units complement contained in 0.2 ml. After overnight incubation at 4 C, 0.2 ml sensitized sheep cells was added to all tubes, followed by another incubation

period of 15 to 20 minutes at 37 C. Appropriate controls were included with all tests. Concurrent titrations with control serum insured the maintenance of antigen titer. A number of sera were tested again in modifications of the complement fixation test without alterations of results.

Antigens for Skin Tests: Approximately 30 different batches of antigen were prepared and distributed. Suppurative material obtained under sterile conditions was diluted in saline 1 : 5 and homogenized in a blender. The homogenate was heated at 60 C for two hours, and again on the following day for one hour, after overnight refrigeration. Bacterial sterility tests were then carried out in routine bacteriologic media and in suckling and adult mice. The material was stored in vials with rubber stoppers at 4 C. Many of the preparations were still significantly antigenic after storage in this manner for at least three years.

Sterility tests for possible inclusion of hepatitis virus were not attempted. Screening of all donors for a history of hepatitis remains the only known protective device against this group of agents.

Before introducing new lots of antigen for skin tests, such lots were simultaneously tested with a known preparation. Variations in capability of producing erythema were frequently encountered. Two lots were discarded because they failed to produce a recognizable area of erythema when tested along with known positive antigens.

Skin tests were performed by intradermal injection of 0.1 ml antigen into the forearm. Readings were made at both 24 and 48 hours, since variation in time of appearance of reactions has been repeatedly encountered. Any area of erythema, regardless of size, was considered positive. Induration alone, on the other hand, was considered of questionable significance. Immediate reactions, which did not persist, were considered negative.

Results

SEROLOGIC

All serologic tests were performed without prior knowledge of the results of the skin test. When quantities permitted, sera were tested in two different serology laboratories, where similar results were obtained.

Of the 130 pairs of acute and convalescent sera tested with the psittacosis-lymphogranuloma venereum group antigen, six showed a fourfold rise or higher in complement fixation antibody (Table 1). Twenty-four other patients manifested detectable titers, 12 of which were at the level of 1 : 4. Four patients demonstrated titer increases of doubtful significance. In contrast, 96 patients failed to exhibit detectable antibody to this antigen. As can be seen in Table 1, the results obtained by testing the 40 single specimens were approximately the same as obtained with paired sera. Three per cent (six of 200) of the control sera indicated complement fixation antibody to the group antigen, and these were all either at the 1 : 4 or 1 : 8 level.

The titers observed in individuals exhibiting antibody responses are difficult to interpret. Of the 24 patients with antibodies, but without rise in titer, only two

Table 1. Complement Fixation Results on Sera from Patients with Cat-scratch Disease (Positive Skin Reactions)

	No. Tested	No. with Fourfold Rise	No. Doubtful Rise	No. with Stationary Antibody	No. without Antibody
Paired sera	130	6 (4.6%)	4 (3.1%)	24 (18.5%)	96 (73.8%)
Single sera	40	—	—	10 (25%)	30 (75.0%)
Controls*	200	—	—	6 (3.0%)	194 (97.0%)

* Randomly selected sera from individuals not skin tested with cat scratch disease antigen.

TABLE 2. Complement Fixation Titers of Sera Demonstrating No Rise in Titer

	Complement Fixation Titer*					
	4	4	8	16	64	Total
Paired sera Acute	2	12	0	8	2	24
Paired sera Convalescent	8	12	0	4	0	24
Single sera	0	7	1	2	0	10
Controls	194	4	2	0	0	200

* Reciprocal of dilution.

had titers of 1 : 64; these were both in the acute phase specimen (Table 2). More patients demonstrated drops in titer between acute and convalescent phase specimens than increases. It is evident that the antibody response, as determined by using a psittacosis-lymphogranuloma venereum group antigen, is of low order. Although not indicated, the initial titers of individuals demonstrating a fourfold or higher antibody difference were also rather low, that is, between 1 : 8 and 1 : 64.

SKIN TESTS

The results of comparative studies of skin tests with different batches of antigen indicated a wide variation in response (Table 3). Of four patients simultaneously tested with antigens No. 1 and No. 2, three were positive with No. 1, whereas all four were equally reactive with No. 2 (test group 1). Similar differences were noted in five patients tested with preparations No. 2 and No. 3 (test group 2). Three patients tested with No. 1 and No. 3 (test group 3) reacted as follows: One was positive with No. 1 and negative with No. 3; the second patient demonstrated the reverse of this, that is, positive with No. 3 and negative with No. 1; the third patient was positive with both antigens. Two patients were tested with No. 6; one of these with No. 2 also, and the other with No. 5 (test group 4). Both of these individuals were positive to No. 6, but negative to the other antigen.

Another test group (group 5) consisted of four volunteers who were simultaneously tested with four different lots of antigens. Two inoculations were given on each arm, but without any predetermined area for any particular antigen. All four patients reacted in a positive manner, although differences in sizes of reactions appeared to three of the antigens (Nos. 5, 6, and 8). However, two of the patients were negative to test antigen No. 3.

More extreme examples of variation to skin test lots were seen with test groups 6 and 8. One antigen, No. 7, was consistently negative on ten of 12 patients. Positive reactions were observed on the donor

TABLE 3. Skin Test Reactions with Preparations of Antigens from Different Patients

Test Group*	Antigen Preparation								
	1	2	3	5	6	7	8	10	11
1	3/4†	4/4							
2		4/5	5/5						
3	2/3		2/3						
4		0/1		0/1	2/2				
5			2/4	4/4	4/4		4/4		
6						2/12	10/12		
7						0/5	5/5	5/5	
8								6/25	23/25
Total	5/7	8/10	9/12	4/5	6/6	2/17	19/21	11/30	23/25

* Each test group was simultaneously tested with the designated antigen preparations. See text for full explanation.

† Numerator = number of individuals positive. Denominator = number of individuals tested.

of the suppurative material only, and another completely unrelated patient. Antigen No. 8 was positive in ten cases, but negative on the two patients reacting with No. 7 antigen. Five patients tested with antigens Nos. 7, 8, and 10 reacted only to Nos. 8 and 10 (test group 7). Equally indicative of the variation in response to different antigens for skin tests were the findings in test group 8 with Nos. 10 and 11. After assuming that lot No. 10 was satisfactory (based upon results obtained with antigens used in test group 7), 25 patients subsequently were simultaneously tested with these two antigens. Of the 25 patients in the group, four were positive with both Nos. 10 and 11; 23, including the four also positive with No. 10, were positive with No. 11; and two patients were positive to No. 10, but negative to No. 11.

Interpretation of these results does not permit a reasonable conclusion. It may be noted that all antigens were tested in at least two different test groups. In some instances, good correlation between antigens from different patients utilized in a given test group was obtained; however, exceptions were noted. Although any reaction, regardless of size of erythematous area, is considered positive as indicated above, it is obvious that extreme variations in size of reaction may be encountered. In certain instances, patients responded with barely detectable wheals (measurable in millimeters), whereas others reacted to a marked degree. Large, erythematous reactions, measurable in centimeters or inches, were frequently noted. Not infrequently, a reaction similar to that observed at the site of the scratch, such as the development of a papule, was seen. These, at times, left permanent scars at the site of the skin test. It is highly probable that, in most instances, individual differences in sensitivities account for the variations observed. The results obtained, however, may also be interpreted as antigenic differences among the preparations.

SKIN TESTS OF PATIENTS WITH LYMPHOGRANULOMA VENEREUM

An attempt was made to define the relationship of cat-scratch disease to the psittacosis-lymphogranuloma venereum group of agents by skin testing patients known to have positive reactions to psittacosis-lymphogranuloma group antigen. Comparisons were made between tests with cat-scratch and Frei antigens. In addition, complement fixation tests with the psittacosis-lymphogranuloma venereum group antigen were performed on sera from these individuals (Table 4). All five patients, four of whom had positive reactions to the Frei test, reacted in the complement fixation test with titers greater than 1 : 10, with a high of 1 : 160. The skin reactions with the cat-scratch antigen were not conclusive; only one patient responded to cat-scratch material with a clearly defined area of erythema. The results on two patients were negative, and on two others, questionable.

Very rarely are questionable reactions observed, inasmuch as any area of erythema is considered positive. It is interesting to note that one patient with a questionable cat-scratch antigen skin test was negative with the Frei antigen, but had significant demonstrable antibody to the complement fixation group antigen. One may speculate, inasmuch as definitive information is not available, that the Frei test in this individual was negative as is seen in early cases, or perhaps was reversed as the result of

TABLE 4. Cat-scratch Skin Tests, Frei Tests, and Complement Fixation Results on Lymphogranuloma Venereum Patients

Patient No.	Cat-scratch Skin Reaction	Frei Test	Complement Fixation Test
1	+	+	1:160
2	±	−	1:160
3	−	+	1:80
4	?*	+	1:20
5	−	+	1:10

* Negative until the seventh day, then positive.

cortisone therapy. The other questionable patient may have been a case of delayed sensitivity in response to the skin test material. Such delayed reaction would be similar to that reported by McGovern, Kunz, and Blodgett (11) in which induration and erythema were not observed until five to nine days after administration of the skin test.

Discussion

In favor of a relationship between cat-scratch disease and the psittacosis-lymphogranuloma venereum group of diseases is the continued relatively high incidence of patients demonstrating antibodies to the group antigen. The experience of several laboratories reporting complement fixation results indicates a greater frequency of psittacosis-lymphogranuloma venereum group antibodies among patients with cat-scratch disease, than among control groups (Table 5). In certain instances, the numbers involved are too small to be significant. However, it is apparent that there is generally a greater frequency of reactions among patients having cat-scratch disease than among normal persons. If, on the other hand, the antigenic relationship was close to that of the psittacosis-lymphogranuloma venereum group of agents, then one would expect to see among patients with cat-scratch disease a still greater prevalence of group antibodies, as well as a greater number of individuals demonstrating fourfold (or higher) antibody increases. Few reporting laboratories indicate antibody increases when performing serologic tests on sera of patients with cat-scratch disease. Apparently most laboratories are satisfied with the mere demonstration of antibody rather than the conventionally accepted fourfold antibody rise. It is recognized that cat-scratch disease is a chronic illness, fre-

Table 5. Results of Survey of Literature on Patients with Cat-scratch Disease Tested for Complement Fixation Antibody to the Psittacosis-Lymphogranuloma Venereum Group of Viruses

Investigator	Source of Sera	Total No. Tested	No. Positive	Per Cent Positive*
Manning and Reid (9)	Patients	35	8	23.0
	Positive pathology	10	6	60.0
	Negative skin test	44	0	0.0†
	Controls	204	4	2.0
Armstrong et al. (8)	Patients	40	8	20.0
	Controls	71	8	11.3
Mollaret et al. (5)	Patients	43	20	46.5
Daniels and MacMurray (2)	Patients	12	3	25.0
Kalter et al. (3)	Patients	22	7	31.8‡
Morrissey (10)	Patients	10	7	70.0
Gifford (12)	Patients	4	1	25.0§
	Negative skin test	5	2	40.0
Waters, Kalter, and Prior (13)	Patients	4	2	50.0
Spaulding and Hennessy (4)	Patients	39	14	35.9
	Controls	120	0	0.0
Kalter	Patients	170	44	25.8
	Controls	200	6	3.0

* A titer of 1:10 or higher.
† One individual had a titer of 1:5.
‡ Five individuals had a titer of 1:5.
§ Veterinarians.

quently resulting in the physician's seeing the patient late in the clinical course of the disease. It would appear, however, that the number of cases with demonstrable antibody changes is fewer than expected. A greater number of individuals with antibody rises would be anticipated, after time has elapsed to permit antibody response. The majority of patients with positive skin tests, in contrast, do not manifest complement fixation reactivity. It is conceivable that individuals with a complement fixation response have been in contact with an agent antigenically related to the psittacosis-lymphogranuloma venereum group. The agent, although related to this group of viruses, may at the same time be one of several comprising a spectrum of cat-scratch disease. Complement fixation reactions may also be anamnestic, rather than primary, due to the presence of one or more antigens common to the psittacosis-lymphogranuloma venereum group or, conceivably, may be nonspecific reactions.

Attempts to obtain further information on the relationship between cat-scratch disease and the psittacosis-lymphogranuloma venereum group of virus illness by skin testing lymphogranuloma venereum patients were not too rewarding. The number of patients involved was too small for clarification. Generally speaking, it is recognized that patients having cat-scratch disease do not respond to the Frei antigen. The results reported here reveal that a number of patients with lymphogranuloma venereum similarly do not react to cat-scratch disease antigen for skin tests.

Additional difficulties arise when antigen for skin tests is employed as an aid in final diagnosis. Most noteworthy are the variations in response of patients to different preparations of test antigen. In addition, individual variations to a given material for skin tests have become well recognized. Usually, this material has been too limited to allow detailed evaluation. McGovern et al. (11) reported that their patients reacted positively with all antigens employed, although variations in intensity of erythema were described. The data reported here, while still limited, disclose not only variations in intensity of reaction among patients, but the complete failure of certain individuals to respond to one or another of the test preparations. The differences observed in the comparative testings also suggest the possibility that more than one strain of "virus" exists. One antigen preparation (No. 4) was discarded after tests on three individuals were negative. In retrospect, perhaps a more extensive testing of patients may have yielded results similar to those observed with other lots (Nos. 7 and 11). The recent report of a hemagglutination test (7), if confirmed, may help to differentiate the variations noted above. Further attempts to correlate serologic response with reactions to skin tests are indicated.

Final clarification of this problem awaits isolation of a specific agent, or at least a serologic test capable of detecting antibody changes. The data described here suggest that more than one agent is responsible for the disease. If one agent is responsible, then antigenic relationship between strains is probably remote. Continued study of this entity, especially the diagnostic considerations, is necessary. For practical purposes, it is now suggested that antigen pools be used for skin testing in order to diminish the probability of negative reactions.

Conclusions

The results reported here on the serologic responses of patients with cat-scratch disease to the psittacosis-lympogranuloma venereum group antigen substantiate those previously described. A group of 130 patients positive to skin tests demonstrated a 26.2% complement fixation antibody response to the group antigen. This figure is consistently higher than figures obtained or reported for normal control groups. In addition, variations in reactions to skin

tests were observed with different preparations of test antigen. These variations extended from complete failure to produce an area of erythema to marked differences in size of reaction. Because of this extreme variation in reactivity, it is recommended that antigen for skin tests be derived from pooled material in order to decrease the probability of obtaining variable response.

The response of a number of patients with production of psittacosis-lymphogranuloma venereum group antibodies, and the marked variation in response to different preparations of antigen for skin tests observed in other patients, suggest the possibility that more than one agent is responsible for the syndrome referred to as cat-scratch disease. Antigenic overlapping with the psittacosis-lymphogranuloma venereum group may account for the relatively high incidence of serologic reactivity among cat-scratch disease patients.

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Summario in Interlingua

Datos serologic e de tests cutanee es presentate pro un gruppo de patientes con maladia de ungues de catto, con le objectivo de demonstrar un relation possibile con le gruppo de virus de psittacosis e lymphogranuloma veneree. Es date in plus le resultatos de tests cutanee effectuate in le patientes con differente lots de antigeno.

Le datos obtenite indica que le incidentia de positive reactiones serologic con iste antigeno de gruppo es uniformemente plus alte que in le gruppo de controlo. Tamen, le procentage de resultatos positive es infra le nivello on expectarea a base de un directe relation causal. Le responsas de gruppos de subjectos a differente preparatos de antigeno de test cutanee esseva si variabile que on debe supponer (1) que plus que un agente es interessate in le condition o (2) que marcate variationes de racia occurre in le agentes que produce lo. In un pauco numerose gruppo de patientes con lymphogranuloma veneree, duo inter cinque non respondeva per positive reactiones cutanee quando illes esseva testate con antigeno de maladia de ungue de catto, e al minus duo del remanente tres respondeva in un maniera que non permitteva un interpretation inequivoc. In vista de iste constatationes, le these es presentate que maladia de ungue de catto pote esser causate per plure agentes e que un de illos es relationate antigenicamente con le gruppo de virus de psittacosis e lymphogranuloma veneree.

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"Purple Toes": an Uncommon Sequela of Oral Coumarin Drug Therapy

WALTER FEDER, M.D., and ROBERT AUERBACH, M.D.

Chicago, Illinois

THE UTILITY OF COUMARIN TYPE ANTICOAGULANTS during the acute stage of many types of thrombo-embolic incidents, including myocardial infarction, has been well established clinically. More recently, the efficacy of these drugs for long-term prophylaxis has also been shown to be of value (1–4), and there is an increasing population of patients on long-term oral anticoagulant therapy. The purpose of this paper is to describe a dermatologic side effect of such therapy, which, to the best of our knowledge, has not been reported previously.

Our attention was directed to six patients who developed a dark blue-tinged bilateral purple discoloration of the feet, especially the plantar surfaces and the sides of the first two toes. This was sometimes preceded or accompanied by a red-tinged violaceous nondescript discoloration of the thenar and hypothenar eminences of the hands. In one of these patients, only the hand changes were present. These lesions, which we have called "purple toes" because the toe lesions are more striking, have the following in common: [1] They develop three to eight weeks after the patient is started on treatment with either bishydroxycoumarin (Dicumarol®) or warfarin; [2] at the time the lesions appear, the prothrombin times (one-stage Quick method) are all in the therapeutic range, i.e., 1.75 to 2.5 times the control time, and there is no clinical or laboratory evidence of epistaxis, hematuria, blood in the stools, hemoptysis, or other type of hemorrhage; [3] the color blanches completely on moderate pressure, thereby distinguishing these lesions from hematomata and purpura; [4] the color fades but never disappears when the legs are elevated 90° from the horizontal; [5] the toes are symptomatically painful and tender on palpation; [6] the intensity of the discoloration and tenderness may wax and wane but the color changes persist indefinitely.

The patients were all white males, and there was a wide age range of 53 to 69 years. They constituted about 1% of our outpatient population on long-term oral anticoagulants, consisting of 331 males and 119 females. Bromsulphalein excretion in these patients was mildly elevated in two instances, normal value being 0 to 7% retention of the dye at the end of 45 minutes.

Three of the six patients have had diabetes mellitus, whereas blood sugars in the other three have been within normal limits to date. Biopsy specimens obtained from the skin in an involved area in four patients did not add any significant information.

CASE REPORTS

S. O., a 53-year-old male, was first seen at The University of Chicago Clinics in November 1960 and a diagnosis of hypertensive arteriosclerotic cardiovascular disease with congestive heart failure was made. A diabetic glucose tolerance curve was noted. Bromsulphalein injection showed 12% retention of the dye after 45 min-

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From the Department of Medicine, University of Chicago, Chicago, Illinois.

Requests for reprints should be addressed to Walter Feder, M.D., Department of Medicine, University of Chicago, 950 East 59th Street, Chicago 37, Illinois.

FIGURE 1. Appearance of feet five weeks after patient started bishydroxycoumarin. Both the plantar and dorsal surfaces of the feet are involved, particularly the pressure areas. It is possible to discern these lesions even in black and white photographs.

utes. The patient was treated with digitalis and 3 g sodium chloride diet.

In December 1960 he was re-admitted with weakness of the right arm and aphasia because of cerebral artery insufficiency for which bishydroxycoumarin therapy was instituted. About five weeks later, he noted that his toes were markedly tender when his bed covers touched them. When we saw him in April 1961, the plantar surfaces and sides of all his toes were dark blue-purple and blanched completely on pressure and lightened on elevation. They have become progressively more tender. Biopsy of the lateral side of the right fifth toe showed hyperkeratosis compatible with the skin site. There was no inflammation or hemorrhage; his peripheral pulses were normal. His prothrombin time, when the lesions developed, ranged between 20.5 and 32 seconds (control 12.6 seconds).

M. H. B., a 69-year-old white male, had been treated for diabetes mellitus since 1957, at first with diet and variable small amounts of isophane insulin and subsequently with tolbutamide, 1 g daily. He was admitted to the hospital in October 1959 for congestive heart failure and treated with digitalis. In July 1960, he suffered a thrombosis of a branch of the right middle cerebral artery; treatment with bishydroxycoumarin was started.

Five weeks later he noted a violaceous discoloration of the toes which progressed up to his iliac crest. His prothrombin time during this period was 26 to 27 seconds with a control time of 12 seconds. Examination showed a deep purple discoloration and mottling of his feet bilaterally, most marked on the first two toes and the plantar surfaces. This appeared in a lighter color over the other toes and the rest of the foot, and in a thick-lined serpiginous pattern over his legs and buttocks anteriorly and posteriorly (Figures 1 and 2). The toes were tender. All the involved areas blanched completely on pressure, and became lighter on elevation of the legs. There were no signs of inflammation, and the peripheral pulses in his legs were palpable although not strong. A red-purple discoloration of the palms and fingers was also noted. There was no hematuria or other clinical evidence of hemorrhage. Biopsy of an involved area on one buttock showed some hemosiderin in the upper dermis. His bromsulphalein retention was 7%.

Because of increasing complaints of tenderness in the feet and toes, the drug was discontinued for a month during which time the patient was maintained on heparin, 400 mg injected subcutaneously once daily. His prothrombin time dropped to 15 seconds (control 12.6 seconds) during this interval; and although the lesions became lighter and the toes less tender, both persisted in a mild form. Warfarin was then administered with resultant exacerbation of the tenderness and deepening of the discoloration which has persisted to date.

FIGURE 2. Note serpiginous character of lesions extends over the legs in the same patient as shown in Figure 1.

A. D. was a 66-year-old white male who was first admitted to the hospital in 1949 with a long history of ulcer distress; the diagnosis of an active duodenal ulcer was confirmed roentgenographically. He was re-admitted in 1951 with a recurrent ulcer and massive gastrointestinal hemorrhage. In March 1960, he was admitted for an acute myocardial infarction and was treated with warfarin. At the time of discharge five weeks later, this medication was continued, and meprobamate, phenobarbital, and belladonna were to be taken as needed. Shortly thereafter, he noted a discoloration of the first toes of both feet. He had a marked dark purple diffuse discoloration of both first toes and similar lesions which were not as dark on the other toes, all of which blanched completely on pressure (Figure 3). The toes were tender but there was no inflammation and no epidermal change. The palmar and plantar surfaces showed increased erythema. His prothrombin times were well controlled daily throughout hospitalization and in the period following discharge, varying from 21 to 29 seconds (control 11.5 to 12.9 seconds). The dermatologic lesions have persisted. In January 1961 his bromsulphalein retention was 4% and his two-hour post-prandial blood sugar was 90 mg/100 ml.

O. E., a 61-year-old white man, had a myocardial infarction in 1957. At that time, he was not treated with anticoagulants but was given diuretics and pentaerythritol tetranitrate. He was seen at our clinic for the first time in September 1959, at which time he was considered to have arteriosclerotic hypertensive cardiovascular disease with congestive heart failure. In addition, the diagnosis of polycythemia rubra vera was made because of markedly elevated hemoglobin, red blood cell count, and hematocrit. After a phlebotomy of 500 ml, the blood counts reverted to normal and remained so thereafter. He was also treated with digilanid and warfarin.

In December 1959 he complained of pain in the fifth toe of the left foot. Both this toe and the first toe were blue-black and blanched com-

FIGURE 3. Patient experienced tenderness and a purple-blue discoloration of toes and lateral sides of the feet within two months after starting warfarin therapy.

pletely on pressure. The lateral and plantar surfaces of both feet were then involved, showing the dark purple discoloration without epidermal change; this involvement extended to the knees. The toes and sides of the feet were markedly painful and tender. He also had the red-tinged violaceous discoloration of the thenar and hypothenar eminences of the hands. At the time the lesions developed, all his prothrombin times were within the therapeutic range and averaged 23 seconds (control 12.2 seconds). It was decided to change the oral anticoagulant from warfarin to bishydroxycoumarin in January 1960, but there was no subsequent improvement in his feet or hands.

He was re-admitted in April 1960 because of chronic congestive failure and weight loss. At this time, the additional diagnosis of diabetes mellitus was made. Chlorothiazide was added to his regimen. The discoloration was still present when he died suddenly of massive gastrointestinal bleeding on September 25, 1960.

L. Z. was a 56-year-old white married male with arteriosclerotic cardiovascular disease who had had an acute myocardial infarction on August 14, 1960. Anticoagulation with warfarin was started the next day. Approximately six weeks later the patient noted a bluish-red asymptomatic discoloration over the thenar and hypothenar eminences and the anterior metacarpophalangeal joints of both hands. The prothrombin time averaged 21 seconds (12 seconds control). These joints blanched completely with pressure and the condition has persisted without change. Bromsulphalein dye injection in January 1961 showed 9% retention. There was no history of alcoholism or liver disease. Fasting blood sugars on two occasions were 55 and 82 mg/100 ml. Biopsy of the palmar lesion showed thick corneal and malpighian layers as would be expected in this location. The capillaries were dilated but there was no specific change.

J. E. A. was seen for the first time in June 1957 with a history of two previous myocardial infarctions and exertional dyspnea, angina pectoris, and pedal edema of three years' duration. At this time, his maintenance digitalis dose was adjusted and treatment with bishydroxycoumarin started. Several weeks later, he developed erythema of the thenar and hypothenar eminences of both palms which has persisted to date. This erythema blanches completely on pressure; no tenderness has ever been present, and there are no epidermal changes. When this lesion developed the prothrombin time was within normal range.

During the next four years he had numerous hospitalizations elsewhere and six hospitalizations at The University of Chicago Clinics for congestive failure and recurrent right middle lobe pneumonitis. In September 1958 his oral anticoagulant was changed from bishydroxycoumarin to warfarin at another hospital. In February of 1961, he was admitted for the seventh time because of a grossly hemorrhagic stool. His prothrombin time was 25.1 seconds (control 12.7 seconds). During the first two days of the hospitalization, his stool reverted to normal form and consistency and the bleeding and abdominal discomfort lessened and ceased; no explanation for the bleeding was found despite extensive examinations. On his seventh hospital day, he developed a mottled purplish discoloration on the toes and soles of both feet and these areas were tender. His prothrombin time ranged from 18 to 26 seconds (control 11 to 12.7 seconds). With bed rest, the lesions became less severe by the time of discharge on the seventeenth hospital day. Biopsies of the palm as well as an involved area of the foot were normal. The bromsulphalein test showed 4% retention; two-hour post-prandial blood sugars on different occasions were 83 and 107 mg/100 ml.

Discussion

Previously reported dermatologic effects from coumarin derivatives, other than ordinary hemorrhage, are: [1] urticarial reactions (5); [2] "pruritic maculopapular erythematous eruptions" (6); and [3] a peculiar hemorrhagic necrosis of the skin (7–16). The first two no doubt belong to the morphological changes classified as toxic eruptions. The third effect merits discussion.

Verhagen and Wiersema in 1952 (7) were the first to bring together a series of cases of hemorrhagic necrosis of the skin in the lower half of the body in patients treated with oral anticoagulants for thrombophlebitis. Subsequently Verhagen reviewed an expanded series (8) and other case reports have appeared in the Scandinavian literature (9–16). All of these cases were described as sudden hemorrhages developing in the skin and extending to subcutaneous tissues. In one case (16) erythema was noted, with petechial hemorrhages occurring before the large solid area of hemorrhage; in

the other cases, the hemorrhagic zone was surrounded by hyperemia. Bullae developed in the hemorrhagic area in some patients, and all developed a necrotic zone. The lesions were reported as occurring three to eight days after anticoagulation therapy was begun.

All the authors describing this phenomenon do not believe this is merely another hemorrhagic manifestation of anticoagulation treatment because the prothrombin time is not specifically related to the onset of the lesion. Several had prolonged prothrombin times with other clinical evidence of hemorrhage, while others had times well below the therapeutic range, less than 1.3 times the control value.

They also point out that these lesions did not worsen in those patients in whom anticoagulation was continued, and all cases healed within three months. The indication for anticoagulation in all the cases was thrombophlebitis, except for the case of myocardial infarction reported by Mikelsen (10), who reported the only biopsy description of such as a "hemorrhagic necrosis." He stated that in a biopsy taken one week after the appearance of the lesion, and in another specimen taken at autopsy, the microscopic examination showed subcutaneous hemorrhage and dilated capillaries with shrinkage and pyknosis of endothelial cells. These specimens may have been taken too late to show the primary lesion.

The development of "purple toes" is clearly different from these other types of dermatologic conditions as is obvious from our previous description of the nature and course of these lesions. It may be differentiated also from acrocyanosis in that the latter occurs in girls and young women in 90% of the cases, usually occurs on the hands and only occasionally on the feet, and is asymptomatic (17). All of our cases of "purple toes" have occurred in men, the lesions in the feet are more prominent, and they are painful and tender. Five biopsy specimens taken from four of our six patients showed hemosiderin in one specimen (common for this location), dilated capillaries in the dermis of another specimen, and no changes in the other three.

The etiology of the lesions in our patients is basically unknown but several lines of evidence can be converged to suggest possible mechanisms. Previous experimental work has shown that the coumarin drugs have direct effects both on capillaries and on cells independent of their effects on the clotting mechanism. It has been demonstrated that bishydroxycoumarin increases capillary permeability and capillary resistance before the prothrombin time is prolonged, and that such effects persist after the drug is stopped and the prolonged prothrombin time returns to normal (18–21). In cells grown in tissue culture, coumarin has a direct cytotoxic effect (22). The mild antibiotic effect of bishydroxycoumarin in inhibiting the cellular growth of bacteria is also evidence for a cytotoxic effect (23). There has also been some work to indicate that the drug has a vasodilating action presumably by an effect on smooth muscle (24, 25). It would seem to us that direct capillary and cellular damage as well as vasodilation might account for the vascular lesions we have described. However, the time lag of three to eight weeks before the lesions appear and the fact that they are so uncommon raises doubt as to whether these mechanisms alone would explain this phenomenon. Perhaps it is also necessary to incriminate an effect on the blood clotting mechanism.

Evidence has been accumulating for the past several years that during treatment with coumarin drugs clotting factors IX (plasma thromboplastin component) and X (Stuart Prower factor) may be abnormally depressed (26, 27) in addition to factors VII and prothrombin. Various studies have shown a dissociation between the one-stage Quick test in the therapeutic range and the extent to which the first two factors may

or may not be deranged in patients taking oral anticoagulants (28–30). It is conceivable that the other effects previously mentioned must combine with an effect on factors IX, X, or both to produce "purple toes." Further work is currently being undertaken to test these hypotheses.

Summary

Six cases are presented with a cutaneous vascular lesion occurring three to eight weeks after anticoagulant therapy with coumarin derivatives was begun. These are differentiated from other dermatological effects which have been observed in the course of anticoagulant therapy, and possible mechanisms for their production are suggested.

Acknowledgments

We wish to acknowledge our gratitude to Emmet B. Bay, M.D., Richard J. Jones, M.D., and Louis Cohen, M.D., each of whom called our attention to one of his patients with the lesions we have described. We are also indebted to them and to Allan Lorincz, M.D., for reviewing this manuscript. To Brian Potter, M.D., we owe our thanks for his assistance with the microscopic evaluation of the biopsy specimens.

Summario in Interlingua

Es describite lesiones de vasculatura cutanee occurrente in sex patientes post therapia anticoagulante a derivatos de coumarina. Detalios del casos es presentate. Le lesiones consiste de purpureo-blauastre discolorationes bilateral in le pedes, specialmente le superficies plantar e le lateres del prime duo digitos. Isto esseva precedite o accompaniate in plure casos per un indefinite discoloration rubio-violacee del eminentias thenar e hypothenar del manos.

Le lesiones ha le sequente characteristicas in commun: (1) Illos se disveloppa tres a octo septimanas post que le patiente comencia le tractamento con Dicumarol® o con warfarina; (2) al tempore del apparition del lesiones, le tempores de prothrombina (secundo le methodo uniphasic de Quick) es omnes intra le region therapeutic, i.e., illos amonta a inter 1,75 e 2,5 vices le valores de controlo, e nulle signo clinic o laboratorial es constatabile de epistaxis, hematuria, sanguine in le feces, hemoptysis, o altere typos de hemorrhagia; (3) le coloration reage per un blanchimento complete a moderate grados de pression; (4) le coloration se attenua, sin unquam disparer completemente, quando le gambas es elevate a un angulo de 90° ab le plano horizontal; (5) le digitos del pede es symptomaticamente dolorose e hyperesthetic sub palpation; e (6) le intensitate del discoloration e del hypersensibilitate pote accrescer e decrescer, sed le alteration del color persiste indefinitemente. Specimens bioptic obtenite ab le pelle in un area interessate in quatro del sex patientes non augmentava le information significativemente.

Le lesiones designate como "digitos purpuree de pede" es differentiate ab altere effectos dermatologic que ha essite observate in le curso de un therapia a anticoagulante. Es proponite possibile mechanismos in lor production.

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Mycobacterial and Mycotic Antibodies in Sera of Patients with Sarcoidosis

Results of Studies Using Agar Double-diffusion Technique

JOHN S. CHAPMAN, M.D., F.A.C.P., *Dallas, Texas*

IN THE OFFICIAL PRONOUNCEMENT of the Committee on Sarcoidosis of the National Research Council, sarcoidosis is a "disease of unknown etiology." This view is not universally accepted. Since Pinner's description of sarcoidosis as an anergic form of tuberculosis (1), a view most notably seconded by Scadding (2), discussion has involved not only the tuberculous etiology, but also the possibility that ultimately the condition known as sarcoidosis may result from identical reactions to many different agents. The multitudinous possibilities have been ably expounded by Refvem (3).

In general, American authors have agreed with the opinion of Lofgren (4) that sarcoidosis is not a form of tuberculosis, though *Mycobacterium tuberculosis* may, on occasion, produce a hard tubercle. Their belief has been based on epidemiological factors, the most cogent of which perhaps are a peculiar geographic distribution in the United States (5) and a constant or rising incidence of sarcoidosis associated with rapid decline in the attack rate of tuberculosis.

If tuberculous infection is not the "cause" of sarcoidosis, the problem still remains that Boeck's disease may be a symptom-complex rather than an entity. If it is a symptom-complex, the etiological agents will be numerous and diverse, and there should be no element common to a large majority of cases. As Siltzbach (6) has demonstrated, however, one common trait shared by some 75% of cases is a positive response to Nickerson-Kveim antigen of good potency.

American investigators, pursuant to their assumption of a common etiological factor in a majority of cases, have started their research on the problem of etiology from epidemiological indications of a heavy concentration of sarcoidosis in rural southeastern United States. The first hypothesis advanced related to beryllium content of the soil of that area (7), while Cummings and Williams looked, rather, toward the flora of the region and were impressed by correlation of pine forest and sarcoidosis (8).

The present investigation was prompted by the development of a workable grouping of acid-fast organisms by Timpe and Runyon (9), the recognition of clinical disease caused by certain of these organisms (10), and the demonstration by Edwards and Palmer (11) of a preponderance, in the southeast, of reactors to a purified protein derivative of a strain of mycobacteria isolated in Georgia.

While the work of Edwards and Palmer with purified protein derivative-B suggested a geographic correlation between the highest incidence of reactors to this antigen and the highest prevalence of sarcoidosis,

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From the Department of Internal Medicine and the William Buchanan Laboratory of The University of Texas Southwestern Medical School.

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Requests for reprints should be addressed to John S. Chapman, M.D., Division of Postgraduate Education, The University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas 35, Texas.

investigation in other areas indicated at least a clinical preponderance of infection caused by other varieties of mycobacteria, notably the Group I or photochromogenic strains (12). Group II, the scotochromogenic organisms, seemed to be less frequently the agents of human disease. Group III, the nonphotochromogens, of which the Palmer strain is a member, produced human infection, while Group IV mycobacteria, marked by their capacity for rapid growth on media, rarely were associated with human disease.

The work of Parlett and Youmans (13) demonstrated that the anonymous mycobacteria produce antibodies in the sera of patients and in rabbit experiments. Accordingly, it was decided to prepare antigens representative of each group of the anonymous mycobacteria, and to determine if antibodies to any of these might be demonstrated in the sera of patients with sarcoidosis. Representative mycotic antigens were included in the battery of tests, since histoplasmosis may produce a picture similar to that of sarcoidosis and since the possibility existed that sarcoidosis might be an unusual manifestation of mycotic infection.

In a preliminary study (14) it was found that when sera of 28 of 32 patients with sarcoidosis were diffused in agar gel they produced two or more bands against mycobacterial antigens prepared from representative strains of the Runyon anonymous groups. Since these 32 patients were all from a limited section of the United States, and since reports of isolations of anonymous mycobacteria have been quite numerous in some parts of the country, an attempt was made to obtain additional sera from other sections of the United States and from foreign countries. The present report continues and expands the preliminary report.

Methods and Materials

Sera from 112 patients with sarcoidosis who reside in 11 states and three foreign countries (Table 1) were available for study. Serum was placed in the central well, and antigens in the peripheral wells of agar plates. One and one-half percent agar was poured in standard Petri dishes and allowed to harden. A second pour of 1% agar was then made, and a tooled plastic template was placed on the agar while it was still soft, resulting in wells of uniform size and uniform distance from each other. The technique is essentially a plate adaptation of Crowle's slide method (15). Strains P-1 and P-8 of Group I, P-6 and P-15 of Group II, and P-2 and P-17 of Group III were obtained through the courtesy of Runyon. Fresh Lowenstein-Jensen media (BBL) transplants of the type strains furnished by Runyon were inoculated into Blake culture bottles containing Sauton's liquid medium.

Table 1. Geographic Distribution of Sera with Reactions

Area	Positive	Negative	Total
France	9	1	10
Sweden	0	5	5
Scotland	7	1	8
New York	3	1	4
Pennsylvania	5	1	6
Washington D. C.	2	0	2
Wisconsin	4	1	5
Virginia	10	4	14
North Carolina	16	2	18
Georgia	5	1	6
Arkansas	0	1	1
Louisiana	7	0	7
Texas	16	5	21
Oklahoma	4	1	5
Totals	88	24	112

The two strains of each group were inoculated into the culture bottles in such a way that each final antigen contained material of two strains of each group rather than a single one.

The bottles of inoculated Sauton's liquid medium were then incubated four to six weeks at 38 C. The fully grown cultures and broth were autoclaved for one hour at 100 C and passed through a Seitz filter. The filtrate was evaporated at 55 C in a Buchler flash-evaporator to one-tenth the original volume. The residual was then passed through filter paper in flowing steam, sterilized in flowing steam at 52 C for one hour each day for three successive days, and transferred to sterile serological bottles.

Concentrated antigens of this type were employed at first, but diffusion was slow and erratic. Because antigens of mycobacteria so

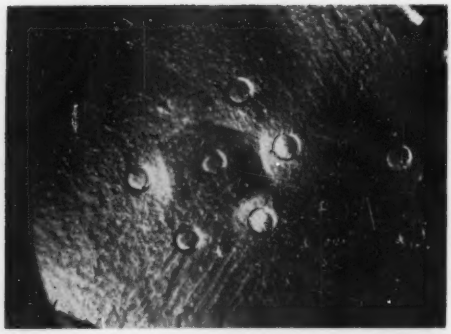

FIGURE 1. Characteristic agar diffusion pattern. Patient's serum is in central well. Antigens, in clockwise order from 12 o'clock are: P-1 and P-8, P-6 and P-15, P-2 and P-17, H37Rv, P-6 alone, P-1 alone. A faint band of identity joins all the anonymous mycobacterial antigens, while heavier individual bands which do not intersect are nearer the wells.

prepared contain large quantities of lipids, it was thought proteins might diffuse more readily through an aqueous gel if lipid materials were extracted. Accordingly, the antigens similar to old tuberculin were shaken with equal volumes of ethyl ether at room temperature and the aqueous phase removed by separation. The resulting solution contained 99% protein, according to analysis. The lipid-free material diffused readily, produced well-defined bands, and was thereafter used for all studies.

Antigen from human tubercle bacilli consisted of standard old tuberculin supplied by the Texas State Department of Health and extracted with ether in the same manner as the other mycobacterial antigens. Mycobacterial antigens were then standardized for protein by the biuret reaction and by electrophoresis.

Two antigens for *Histoplasma* were employed. The first was a standard skin-testing antigen prepared by a commercial firm, while the second was that employed by Furcolow. Coccidioidal antigen was obtained for serological purposes. Antigens from *Cryptococcus* and *Blastomyces* were prepared from strains isolated recently from cases of human disease. Rapidly growing subcultures were inoculated into Sabouraud's broth, incubated for three weeks, and killed by autoclaving. After filtration, the filtrate was concentrated to one-tenth the original volume. Ether extraction, which has proved to be desirable for good study of migration of mycobacterial antigens, was unnecessary in the case of mycotic materials.

TABLE 2. Reactions of Sarcoidosis Serum with Antigens from Anonymous Mycobacteria

Total sera studied	112
No reaction	24
Precipitins observed	88

Readings of precipitation bands were made at 24 and 48 hours (Figure 1).

RESULTS

As indicated in Table 2, 88 of 112 sera (which include those previously reported) produced zones of precipitation when diffused against antigens indicated.

Figure 2 indicates that the sera of 53 patients produced double bands against one or more of the anonymous mycobacterial antigens. Because of multiple reactions, the sum of sera giving both double and single bands is greater than the number of sera found to be positive. The next three columns present the numbers of sera producing single (plain) or double (shaded) bands against individual groups of anonymous mycobacteria. Only two sera produced double bands against antigen of *Mycobacterium tuberculosis,* while seven others produced single bands. There were single bands against fungi in 11 sera, four against cryptococcal, five against histoplasmal, and two against blastomycotic antigens.

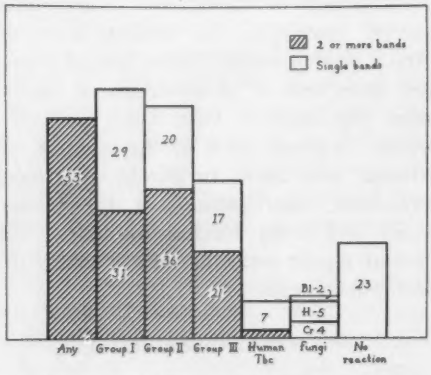

FIGURE 2. Reaction to antigens by extent and by source.

The more extensive collection of sera has a higher percentage of negative reactions (21.4%) than the sera discussed in the preliminary report. A much greater proportion of sera, about 50%, resulted in formation of single zones of precipitation as opposed to the two or more zones found in the positive reactors in the preliminary report. Furthermore, although reactions to Group II organisms were predominant in the original study, they were far less frequent (40%) in the whole series.

Discussion

The significance of a precipitation zone, as noted by Oudin (16), is the presence of an antigen-antibody system. He further observed that the number of zones in agar gel diffusion represented the minimal number of antigen-antibody systems under study. Ouchterlony (17) showed, in addition, that partial cross-reactions may occur when one system is identical in character with one of several systems in an adjacent diffusion.

It has been shown that precipitating antibodies for *Mycobacterium tuberculosis* are present in the sera of tuberculous patients, and that similar antibodies may be induced in rabbits. Parlett and Youmans (13) have demonstrated antigenic relationships among a wide variety of mycobacteria.

Skin tests indicate that many individuals in the United States have had contact with a Group III organism, supposedly P-39 (11). Other antigens for skin testing indicate the probability of multiple mycobacterial sensitization (18). Serological reactions to antigens of different mycobacterial groups may signify, therefore, that an individual has had contact with mycobacteria of more than one group, or, if one or more zones are confluent, that organisms belonging to different groups produce identical antigens. In this study many sera have reacted with antigens from more than one mycobacterial group, while only a few have reacted with antigen of a single group alone. Most reactions to more than one antigen have been of the independent type; that is, when confluence of one of two bands occurs, the other bands will not be confluent.

Since patients with sarcoidosis often exhibit hyperglobulinemia, the presence of antibodies against antigens of the anonymous mycobacteria may indicate no more than a widespread increase in intensity of immune reactions. If this were the correct explanation of these antibodies, a rise in titer or the demonstration of antibodies against more familiar antigens might equally be expected, in which case patients with sarcoidosis should manifest a high frequency of agglutinins against *Eberthella typhosa, Proteus* OX-19, or *Salmonella.* In fact, such reactions are uncommon in previously immunized war veterans (19), as are complement-fixing antibodies against *Coccidioides, Histoplasma,* and *Blastomyces.*

These antibodies may represent an anamnestic serological response produced by an intense but unrelated antigenic stimulus. The low frequency of reactions against *Mycobacterium tuberculosis* antigen (8%) would discount this explanation as would the paucity of reactions against fungus antigens. The point in relation to fungi is particularly pertinent since studies have indicated extensive cross-reactions among fungi (20), including *Candida,* since *Histoplasma* sensitization is common in the United States, and since Heiner (21) has demonstrated that agar diffusion is a very sensitive method for demonstrating antibodies against fungi.

Antibodies against fungi were demonstrable in only 11 of these 112 sera (Figure 2). Of these, four, or nearly half, contained antibodies against *Cryptococcus* only, a very unusual reaction in the experience of this laboratory and a finding of some interest in the light of a recent report (22). Cunliffe (23) has demonstrated additionally that sarcoidosis patients respond less than normals to new antigenic stimuli.

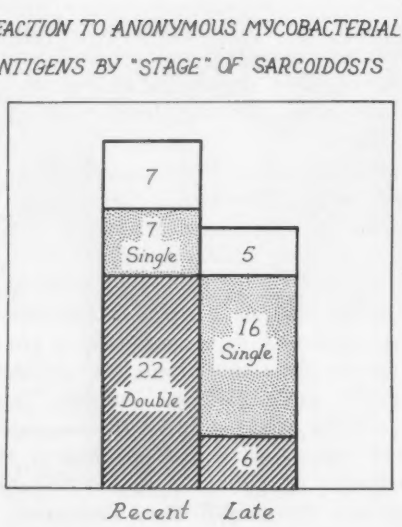

FIGURE 3. Of "recent" patients, 22 had double bands, seven single bands, and seven no reaction against mycobacterial antigens. In late sarcoidosis only six had double, 16 had single, and five had no bands. The number of reactors is less than the total of the series since clinical information was lacking in a number of patients.

The sera of nine individuals who presented marked hyperglobulinemia for other cause, chiefly collagen disease, failed to produce any reactions when diffused against the same group of antigens as were used for sarcoidosis serum, while ten cases with established fungus disease reacted readily with fungus antigens, but not at all with mycobacterial antigens. Other control studies have been discussed in the preliminary report.

Mention was made of the lower reactivity of the entire collection of sera as compared with those in the preliminary report. Several possibilities must be considered. Figure 3 reveals the comparative degrees of reaction between relatively recent cases and relatively older ones. It is evident that the more recent cases present reactions with greater frequency and with more bands than do older cases. Such a difference may result from a decrease in antibodies, or may signify that the antigen employed is incomplete. Fourteen very recent cases had similarly less extensive reaction, seven being entirely negative and seven producing only single zones. In this connection a study of the 24 negative cases, so far as data were furnished, is of some interest.

Five Swedish cases with erythema nodosum were all completely negative. One Scottish serum, drawn when erythema nodosum was present, was positive, though a later serum produced more bands. Three local cases were entirely negative when they

TABLE 3. Patients with Negative Reactions to Antigens of Anonymous Mycobacteria

Number of Patients	Type of Clinical Picture
4	Young Negro children in Virginia with apparent very recent onset.
1	Benign hilar adenopathy and arthralgia three months before serum was drawn.
1	58-year-old female with late stationary sarcoidosis and positive tuberculin.
1	Benign hilar adenopathy only; Kveim positive.
1	38-year-old Negro female with late stationary sarcoidosis and positive tuberculin.
1	30-year-old white female with late active disease and steroid therapy for two years.
2	Negro patients with late active disease and extensive hepatic disease.
1	43-year-old Negro male with hemolytic anemia and very large spleen thought to be sarcoidosis since biopsy of cervical node had been positive three years earlier. He had recently received as much as 1,000 mg prednisolone daily.
1	50-year-old Negro male with earlier biopsy positive and recent cardiac disease thought to be sarcoidosis. He was negative to skin tests with mycobacterial and fungus antigens except Group II to which he responded with 16 mm induration.*

* A reaction to this antigen alone has not occurred in any other of some 300 adults tested.

were first seen, with a syndrome identical with Lofgren's primary sarcoidosis except for the absence of erythema nodosum. Three to nine months later, when roentgenographic evidence indicated clearing of pulmonary lesions, and in one case when the iritis which had been the presenting complaint had subsided, reactions became positive in each. Other negative sera corresponded to the clinical pictures shown in Table 3. One may infer that very early in the development of sarcoidosis no antibodies may be present, that these antibodies rise somewhat later, and that they tend to diminish as the disease enters a late and chronic state, whether inactive or progressive.

The significance of these antigen-antibody reactions in the sera of patients with sarcoidosis is not yet clear. Such reactions, without accompanying reactions to human tuberculosis antigen, have been present in sarcoidosis but not in the present controls and only rarely in the medical students, allergy patients, or sanatorium patients described as controls in the preliminary report. The differences are such as to suggest that agar diffusion in the manner described may be of possible diagnostic use, when considered in conjunction with the entire clinical problem.

It would be very premature to infer an etiological relationship of anonymous mycobacteria to sarcoidosis. The relationships of the antigen-antibody systems involved are very complicated and have not been sufficiently studied to allow any clear inductions. The possibility exists that some other *Mycobacterium* not represented among the strains chosen might contain antigens of higher or more specific reactivity than these. Investigation along these lines is proceeding. The most suggestive data thus far are those indicating an increase in antibodies shortly after the spontaneous remission of primary sarcoidosis and the apparent waning of antibody levels in late disseminated or fibrotic disease. Such variation in the level of antibodies is similar to the fluctuations of complement-fixing antibodies in mycotic disease. Some very few patients with cavitary disease caused by anonymous mycobacteria have also shown precipitating antibodies in agar, while fluctuation in levels of antibodies against *Mycobacterium tuberculosis* has been demonstrated.

That these reactions are found in slightly less than 80% of patients is not surprising since many authorities have considered the possibility that sarcoidosis may represent a common response to numerous agents of disease. This level of response is very similar to that obtained with the most potent Kveim material available (6).

Conclusions

1. Results of agar gel diffusion of sera of patients with sarcoidosis against five anonymous mycobacterial antigens, against human tuberculins, and against antigens of four fungi have been presented.

2. Seventy-eight percent of 112 sera contained antibodies against anonymous mycobacterial antigens.

3. The significance of these findings is discussed in terms of etiology and diagnosis of the disease and of the immunological status of the patient with sarcoidosis.

Acknowledgments

The author expresses his many thanks to Miss Maro Speight, Research Technician II, for her unflagging interest and effort; to J. D. Wilson, M.D., who performed analyses; and to C. E. Smith, M.D., who furnished coccidioidal antigen for serological purposes. He is also most grateful to the following physicians who collected and shipped sera for these studies: Professor John Crofton and Dr. Andrew Douglas, Edinburgh, Scotland; Professor J. Turiaf, Paris, France; Professor Sven Löfgren, Stockholm, Sweden; Dr. M. M. Cummings, Oklahoma City, Oklahoma; Dr. Richard V. Ebert, Little Rock, Arkansas; Dr. Howard Buechner, New Orleans, Louisiana; Drs. Harold Israel and Maurice Sones, Philadelphia, Pennsylvania; Dr. Edwin L. Kendig, Richmond, Virginia; Dr. Louis E. Siltzbach, New York, New York; Dr. Helen

Dickie, Madison, Wisconsin; Drs. Ralph A. Vogel and Ross McLean, Atlanta, Georgia; and Dr. Charles LeMaistre, Dallas, Texas.

Summario in Interlingua

Seros ab 112 patientes con diagnoses clinic de sarcoidosis esseva disponibile pro le test. Le seros veniva ab varie centros in 11 statos del S.U.A. e in Sveda, Francia, e Scotia.

Le seros esseva diffundite in agar, con le uso de un modification a placa del technica a lamina de Crowle anti antigenos mycobacterial representante un racia human de tuberculosis e racias Runyon de Gruppo I, II, e III. Le seros esseva etiam testate contra antigenos mycotic, incluse antigenos de blastomyces, histoplasma, coccidioides, e cryptococcus.

Octanta-octo del 112 seros contineva anticorpore anti le racias Runyon de non-classificate mycobacterios. Novem del 88 etiam possedeva anticorpore anti tuberculosis human e 11 anti un o plures del fungos. Seros ab quatro subjectos monstrava un augmento del magnitude del reaction in tanto que le sarcoidosis primari se meliorava. Le reactiones pareva declinar in magnitude in tanto que le sarcoidosis attingeva tardive stadios inactive o progressive.

Es discutite plure possibile explicationes del presentia de iste anticorpores in le seros de sarcoidosis. Le alte incidentia del reaction es possibilemente de interesse diagnostic e tende a supportar le conception que sarcoidosis es un entitate pathologic.

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The Syndrome of Testicular Feminization

A Report of Three Cases with Chromatographic Analysis of the Urinary Neutral 17-Ketosteroids

A. Louis Southren, M.D., and Akira Saito, Ph.D.

New York, New York

Testicular feminization is a form of male pseudohermaphroditism (1, 2). It includes "females" who appear to be normal, with definite signs of spontaneous gonadal hormone activity at puberty but with male sex chromatin pattern and male gonads. Recently, Jacobs, Baikie, Court-Brown, Forrest, Roy, Stewart, and Lennox (3) described chromosome analysis of bone marrow cells from four such patients, all of whom had a 46/xy chromosomal constitution. The condition is familial and is transmitted exclusively through the maternal line (4). A recent analysis of 16 affected pedigrees supports the contention that this disorder is transmitted by either a sex-linked recessive or a sex-limited dominant mutant gene (4). The demonstration that the gene defect is not closely linked to either of two sex-linked genes such as hemophilia (5) and color blindness (6) tends to favor the latter hypothesis.

Three cases of this syndrome are reported. Two of the patients are "sisters." Included are chromatographic analyses of the urinary neutral 17-ketosteroids.

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From the Endocrine Research Laboratories of the Departments of Medicine and Chemistry, The Mount Sinai Hospital, New York, New York, and the Endocrine Research Laboratory of the Department of Medicine of The Jewish Hospital, Brooklyn, New York.

Requests for reprints should be addressed to A. Louis Southren, M.D., The New York Medical College, 1249 Fifth Avenue, New York, New York.

Methods

The daily urinary neutral 17-ketosteroids were estimated by the colorimetric method of Holtorff and Koch (7). The 3 beta-neutral 17-ketosteroids were precipitated with digitin (8). The remaining 3 alpha-neutral 17-ketosteroids were separated by paper chromatography using the Rubin modification of the Zaffaroni system (9) and identified by the Zimmerman color reaction (10). The solvent system used in our studies was heptane saturated with propylene glycol. The perbenzoic acid oxidation of $\Delta 9^{(11)}$-unsaturated compounds was omitted. This resulted in slightly increased values for androsterone and etiocholanolone. The second chromatogram was made up of three zones: 11-ketoandrosterone, 11-ketoetiocholanolone, and a mixture of the more polar components. The latter consisted of 11-hydroxylated 17-ketosteroids and an unresolved residual fraction. Pregnanediol and pregnanetriol were determined by the methods of Eberlein and Bongiovanni (11) and Bongiovanni and Eberlein (12) respectively. The urinary levels of 17, 21-dihydroxycorticoids were measured by the Peterson modification of the Silber-Porter method (13).

Case Reports

case 1

L. Z., a 34-year-old "woman," was referred for evaluation of primary amenorrhea. The breasts developed spontaneously at 15 years of age. There was no pubic or axillary hair growth

and menstruation did not occur. Several months of cyclic administration of estrogens and progesterone failed to produce withdrawal bleeding. There was a normal heterosexual outlook and normal libido. The siblings included three sisters and five brothers, all of whom were fertile.

On physical examination the patient appeared to be a normally proportioned female. The voice was of normal female pitch. The blood pressure was 160/100 mm Hg. The breasts were well developed, the areolae measured 3 cm across and were adequately pigmented (Figure 1). There was no pubic or axillary hair although hair follicles were present. The clitoris was not enlarged and the labia were normally developed. The vagina ended blindly at 6 cm. Neither the cervix nor the uterus was palpable, but a mass could be felt in the right vault. Speculum examination confirmed the absence of a cervix but demonstrated normal vaginal rugae. A vaginal smear showed the presence of abundant cornified cells.

A skin biopsy was chromatin-negative. Color vision was normal. Twenty-four hour urinary hormonal excretion studies were as follows: neutral 17-ketosteroids were 5.9 mg; 17-hydroxycorticoids, 5.3 mg; pregnanediol, 0.7 mg; and pregnanetriol, 0.4 mg. The urinary gonadotrophin titers were positive at 5 and negative at 50 mouse uterine units. An intravenous pyelogram failed to reveal any gross renal or adrenal abnormalities. At laparotomy, a small centrally located pyriform organ was seen, to each upper outer portion of which was attached a tube-like structure. The distal end of each of the latter was intimately fused with an oval, rather hard mass, resembling a gonad. A small elongated cystic tail-like appendage was attached to each gonad. The entire structure including a section of vaginal epithelium was removed intact.

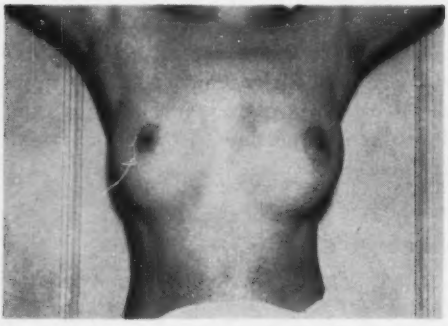

FIGURE 1. *Case 1.* Showing well-developed breasts, areolae and nipples. Axillary hair is absent.

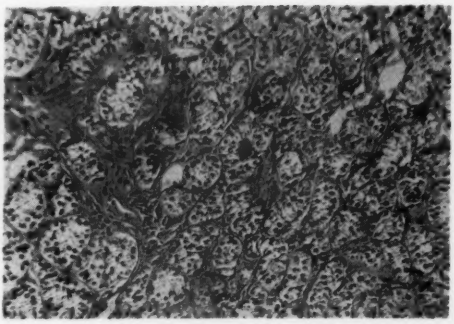

FIGURE 2. *Case 1.* Section of testicular adenoma revealing closely packed immature tubules lined with Sertoli's cells but without spermatogenic elements. Colloid material is seen in one tubule. × 300.

Pathology: The rudimentary mid-line structure measured 3.5 by 2.5 by 1.5 cm and was composed of firm grey-brown tissue. Cross section through the organ showed fibromuscular tissue with numerous vascular channels but without an endometrial cavity or lining. The tube-like structures presented a similar histological appearance. Fimbriae were not present. The left gonad measured 3.8 by 2.5 cm and on cut section was almost completely occupied by a firm, yellow-grey circumscribed mass (3 by 2.5 cm) with multiple small hemorrhages. Histologic examination revealed a testicular adenoma made up of closely packed immature seminiferous tubules filled with Sertoli's cells but without spermatogenic elements (Figure 2). Colloid material was evident in one tubule.

FIGURE 3. *Case 1.* Section of testicular tissue adjacent to the testicular adenoma showing a nodule of Leydig's cell hyperplasia. × 300.

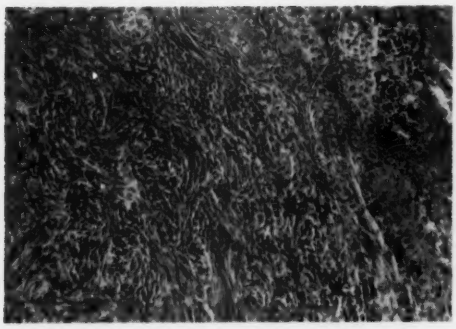

FIGURE 4. *Case 1.* Section of testicular tissue adjacent to the testicular adenoma demonstrating an area resembling cortical ovarian stroma but with a complete lack of primordial follicles or any of their derivatives. × 300.

There was hyperplasia of the Leydig's cells in the area of the testis adjacent to the adenoma (Figure 3). The right gonad was elongated and measured 4 by 1.5 cm. On cut section it consisted of a mass which both grossly and histologically resembled the testicular adenoma noted in the other gonad. Adjacent to the adenoma was an area resembling cortical ovarian stroma but with a complete lack of primordial follicles or any of their derivatives (Figure 4). Histologically the vaginal epithelium was adequately cornified.

Two weeks after gonadectomy the patient began to experience hot flushes and sweats, followed by some breast atrophy, loss of estrin effect in the vaginal smear, and a rise in the urinary gonadotrophin titer to 200 mouse uterine units. The menopausal symptoms disappeared promptly with estrogen administration. The daily excretion of urinary neutral 17-ketosteroids was 6.9 mg (Table 1). The patient was placed on oral estrogen therapy administered cyclically. No significant pubic or axillary hair growth occurred over a four-month interval.

CASE 2

F. R., a 20-year-old "woman," was first seen at 17 years of age with the complaint of primary amenorrhea. Breast development began spontaneously at 12 years of age but no pubic or axillary hair growth appeared, nor did menstrual cycles occur. There was a normal psychosexual outlook. The patient has two sisters; one, age 15 years, is similarly afflicted and is included in the present report as Case 3. The other sibling, age 18 years, had a spontaneous menarche at 12 years of age associated with considerable pubic and axillary hair development. Menstrual cycles have subsequently occurred regularly.

On physical examination the patient was a normally-proportioned female with feminine voice. The areolae were normally developed and pigmented although the breasts were adolescent in size (Figure 5). There was no pubic or axillary hair. The external genitals were normal except for underdeveloped labia. The clitoris was not enlarged. The vagina ended blindly at 4 cm. There was no cervix or uterus; no adnexal masses were palpable. Speculum examination, however, showed a small dimple in the posterior cul-de-sac. The vaginal rugae were normal and a vaginal smear revealed the presence of abundant cornified cells.

A skin biopsy was chromatin-negative. Color vision showed a medium deuteranomaly for red-green using the AO-H-R-R pseudo-isochromatic plates. The younger sister (Case 3) had a similar visual defect. However, the normal sister and both parents had normal color vision. The 24-hour urinary neutral 17-ketosteroid excretion was 7.4 mg, and the urinary gonado-

FIGURE 5. *Case 2.* Note female habitus, adolescent breast development, and absence of pubic hair.

TABLE 1. Chromatographic Analysis of the Neutral 17-Ketosteroids in Each of the Patients

Patient	Medication	Total Neutral 17-Ks.* (mg/24 hrs)	17-Ketosteroid Fractions (mg/24 hrs and (%) of Total 17-Ks*)								
			Beta Fraction	Alpha Fraction							
				Andro.†	Etio.‡	Andro./ Etio.	Total 11-Dexoy-17-Ks. Amt. (%)	11-Keto.-Andro.	11-Keto.-Etio.	More Polar Components	Total 11-Oxy-17-Ks. Amt. (%)
L.Z.	None	6.9	2.0 (29.0)	1.7 (24.6)	0.8 (11.6)	2.1	4.5 (65.2)	0.5 (7.2)	0.3 (4.4)	0.7 (10.0)	1.5 (21.7)
F.R.	None	7.4	1.6 (21.6)	2.8 (37.8)	1.1 (14.9)	2.5	5.5 (74.3)	0.7 (9.5)	0.7 (9.5)	0.6 (8.1)	2.0 (27.0)
P.R.	Estinyl estradiol 0.05 mg/24 hrs	5.5	1.3 (23.6)	1.4 (25.5)	1.4 (25.5)	1.0	4.1 (74.5)	0.5 (9.1)	0.4 (7.3)	0.6 (10.8)	1.5 (27.2)

* Ketosteroids.
† Androsterone.
‡ Etiocholanolone.

tropin titer was positive at 10 and negative at 50 mouse uterine units.

At laparotomy (age 17 years), gonads were seen along the side walls of the pelvis. Overlying each gonad was a tubular structure which was found to enter medially into a rudimentary uterine anlage. A large wedge was removed from the right gonad. Histologic examination of the gonadal tissue revealed immature seminiferous tubules filled with Sertoli's cells but without spermatogenic elements. The interstitial tissue contained an abundance of Leydig's cells (Figure 6).

Subsequently, the patient was placed on oral estrogen therapy. This produced further enlargement of the breasts and development of the nipples. The vaginal tube became more elastic and increased in depth to 7 cm, and the labia enlarged. Pubic and vulvar hair growth occurred but it was largely lanuginous in character. No axillary hair growth was noted. At present, the patient is married and is engaging in satisfactory sex relations.

CASE 3

P. R. is the 15-year-old sister of F. R. (Case 2). Bilateral inguinal hernias were present since the age of two years. On each side a gonad was found within the hernial sac, and both gonads were removed. The operation was combined with an exploratory laparotomy, at which time no uterus was seen, nor were other gonads. Microscopically the gonads were found to be testicles consisting of small seminiferous tubules filled with undifferentiated cells and spermatogonia. No Leydig's cells were seen (Figure 7).

When seen at 11 years of age the patient's general appearance was feminine with normal skeletal proportions and a female voice. There was, however, no breast, pubic, or axillary hair growth. The external genitals were normal except for underdeveloped labia. The clitoris was not enlarged and the vagina ended blindly at a depth of 2 cm. On rectal examination, no internal organs could be palpated. A vaginal smear showed basal and intermediate cells. A skin biopsy was chromatin-negative. Color vision showed a strong deuteranomaly for red-green.

The patient was placed on oral estrogen therapy. This was followed by a steady and progressive response. The breasts gradually developed and the areolae and nipples enlarged and became pigmented (Figure 8). There was, however, only a slight growth of a lanuginous type of pubic and vulvar hair. No axillary hair growth occurred. The labia enlarged and darkened. Graded tube dilatation of the vagina was instituted with lengthening of the vagina to 4.5 cm and some increase in its volume.

FIGURE 6. *Case 2.* Section of right testicle showing immature seminiferous tubules filled with Sertoli's cells but without spermatogenic elements. The interstitial tissue contains an abundance of Leydig's cells. × 600.

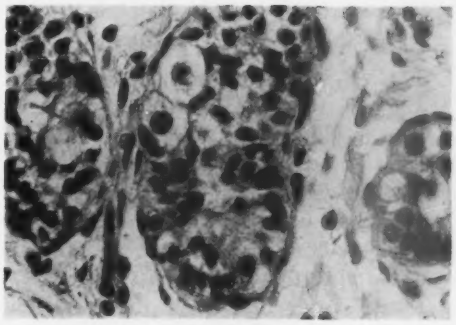

FIGURE 7. *Case 3.* Section of gonad showing immature seminiferous tubules filled with undifferentiated cells and spermatogonia. No Leydig's cells are seen. × 600.

FIGURE 8. *Case 3.* Note the moderate breast development following estrogen therapy. Axillary hair is absent.

Chromatographic Analysis of the Urinary Neutral 17-Ketosteroids

The values for the individual fractions of the urinary 17-ketosteroids are shown in Table 1. Subjects L. Z. and P. R. were studied following castration and P. R. was studied while on estrogen therapy. F. R. was studied prior to castration but after discontinuation of hormonal therapy. In each instance the total urinary neutral 17-ketosteroid excretion was at the lower limits of normal for females at comparable ages. There was no significant decrease in the urinary excretion of the neutral 17-ketosteroids following removal of the gonads in Case 1. The proportion of beta 17-ketosteroids relative to the total was within the upper range of normal. The androsterone : etiocholanolone ratio varied from 1 to 2.5. There was considerable similarity between the various fractions in patient L. Z. (after castration) and F. R. (before castration).

Discussion

The three reported cases represent typical instances of the "feminizing testes" syndrome. The disorder may be suspected by absent or sparse pubic and axillary hair, blind pouch vagina, and primary amenorrhea in apparently normal "females" with normal female external genitals. A chromatin-negative skin biopsy or buccal smear, rudimentary or absent internal female organs and testes confirm the diagnosis. The increased incidence of malignant testicular neoplasms in this syndrome indicates the desirability of early surgical castration. In this regard, removal of testes containing tubular adenomas in Case 1 is significant since the tumors are considered to be premalignant lesions (2).

Feminization in the absence of virilizing features suggests that the testes fail to elaborate appreciable quantities of androgens while secreting adequate amounts of estrogen. In Case 1, the low normal daily urinary excretion of neutral 17-ketosteroids, without any significant decrease following removal of the gonads, indicates that in this patient these compounds are probably extratesticular and presumably adrenal in origin. The similarity in the initial total level and in individual quantities of the 3 alpha steroids in Cases 1 and 2 suggests that these fractions may also be of extratesticular origin in Case 2. It is noteworthy, however, that in two other instances of testicular feminization, the testes appeared to be significant sources of the urinary neutral 17-ketosteroids (14, 15). On the other hand, there is little doubt that the testes are the source of the estrogen. Preoperative estrogen levels have been reported in a number of cases with almost complete disappearance of the compound after orchiectomy (2, 14). The menopausal symptoms in Case 1, following castration associated with some breast atrophy, loss of estrogen effect on the vaginal smear, and a rise in the urinary titer of gonadotropins similarly suggest a testicular source for the estrogens. Chromatographic separation of the neutral 17-ketosteroids in Cases 1 and 2 revealed a predominance of androsterone relative to etiocholanolone although the total amount excreted was within normal limits.

Summary

Three cases of male pseudohermaphroditism with the syndrome of feminizing testes are presented. Two of the patients are "sisters." Chromatographic separation of the neutral 17-ketosteroids revealed an androsterone : etiocholanolone ratio varying from 1 to 2.5. The low normal daily urinary excretion of neutral 17-ketosteroids in Case 1 without any appreciable decrease following removal of the testes indicated that these compounds were probably extratesticular and presumably adrenal in origin. The similarity in the initial total level and individual quantities of the 3 alpha steroids in Cases 1 and 2 suggested that these fractions may also be of extratesticular origin in the latter patient. The finding

of testicular tubular adenomas in Case 1 is significant in view of their probable malignant potential.

Acknowledgments

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Summario in Interlingua

Es presentate tres casos de pseudohermaphroditosmo mascule con le syndrome de "testes femininisante." Duo del patientes es "sorores." Le aspecto clinic esseva characterisate per un predominantia de estrogeno, in despecto del presentia de un configuration mascule de chromatina a gonades mascule. In plus, le symptomas menopausal que occurreva in Caso 1 post castration e que esseva associate con un certe grado de atrophia del mammas, con perdita del effecto de estrogeno in le frottis vaginal, e con un augmento del titro urinari de gonadotropinas suggereva que le testes esseva le fonte del estrogeno. Le separation chromatographic del neutre 17-cetosteroides revelava un proportion de androsterona a etiocholanolona de varie valores inter 1 e 2,5. Le bassemente normal excretion urinari diurne de neutre 17-cetosteroides in Caso 1, que non manifestava un appreciabile declino post le ablation del testes, indicava que iste compositos esseva probabilissimemente de origine extratesticular, i.e., secundo nos, adrenal. Le similitude de nivellos total initial e del quantitates individual del steroides 3α in Casos 1 e 2 suggere que iste fractiones es possibilemente etiam de origine extratesticular in le secunde patiente.

Le constatation del presentia de adenomas testiculo-tubular in Caso 1 es de signification in vista de lor possibile potentialiate maligne.

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The Significance of Fever in Neoplastic Disease

ANN A. BROWDER, M.D., JOHN W. HUFF, M.D., and
ROBERT G. PETERSDORF, M.D.
Seattle, Washington

FEVER IS OFTEN A MANIFESTATION of neoplastic disease, and the literature is replete with case reports of patients who were febrile for months and even years before exhaustive investigation revealed a cryptic neoplasm. Hypernephroma is the prototype of tumor frequently associated with fever and is described in several series of patients with fever of unknown etiology (1–3). Actually, however, fever is a relatively rare symptom of renal cell carcinoma. Israel (4) reported that only 8.2% of 146 patients with hypernephroma were febrile, and Soloway (5) noted pyrexia in eight among his 130 patients. Among 273 patients with renal neoplasms reported by Berger and Sinkoff (6) fever was the presenting symptom in only seven. A similar dichotomy exists in carcinoma of the pancreas in which fever was the presenting symptom in only six of 609 patients (7), yet this tumor is often described as being associated with fever (3).

Boggs and Frei (8) studied the fever of neoplastic disease *in extenso* and found adults with acute leukemia to have fever during 60% of hospital days. Fever was present 26% of the time in Hodgkin's disease, 14% in chronic lymphocytic leukemia, 11% in myelogenous leukemia, and 11% in carcinoma of the lung. Fifty-six per cent of febrile episodes in their patients were unassociated with infection and were presumably due to cancer. The authors also summarized the literature and concluded that fever *not* associated with infection was present in 41% of neoplasms of the stomach, in 66% of carcinomas of the colon and rectum, in 44% of neoplasms of the liver and gall bladder, and in 36% of uterine malignancies. On the basis of these figures, it should be concluded that fever is an extremely common manifestation of malignant disease.

It is our impression, also, that fever and cancer frequently go hand in hand. Of the studies available, only Boggs' places sufficient emphasis on the etiology of fever in cancer, and his patients consisted of a unique group, most of whom had neoplasms of the reticuloendothelial system. The present study is an extension of these observations to adults with cancer admitted to a general hospital in one year. We attempted to determine the frequency of fever in this population, to describe its cause, define its characteristics, and assess its significance. From a pragmatic point of view, this information should provide a more logical approach to the investigation of febrile patients with cancer.

MATERIALS AND METHODS

All patients with histologically proven cancer admitted to the inpatient services of the King County Hospital during 1959 were studied. Their charts were reviewed and the site of the primary tumor, the presence of metastases, the character, height and duration of fever, evidence of bacterial infection, and response to

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From the Department of Medicine, University of Washington School of Medicine, and King County Hospital, Seattle, Washington.

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Requests for reprints should be addressed to Robert G. Petersdorf, M.D., King County Hospital, 325 Ninth Avenue, Seattle 4, Washington.

TABLE 1. Types of Neoplasm

Visceral	126
Esophagus	3
Stomach	15
Large bowel	23
Rectum and anus	22
Liver, gall bladder, biliary tree	8
Pancreas	9
Kidney	2
Lung	35
Primary not identified	9
Pelvic	135
Prostate	65
External genitalia	3
Uterus	8
Cervix	29
Ovary	3
Bladder	27
Miscellaneous	53
Breast	18
Brain	6
Facial structures	8
Mouth, tongue	11
Nasopharynx and sinuses	10
Reticuloendothelial and bone	29
Chronic lymphatic leukemia	6
Chronic myelogenous leukemia	5
Lymphosarcoma	5
Sarcoma of bone	5
Multiple myeloma	6
Acute leukemia	2
Total	343

antimicrobial therapy were recorded. Fever was defined as an elevation in temperature of 99.6 F orally, and 100 F rectally. If fever was present for three successive days, it was termed "persistent"; if days during which the patient was afebrile were interspersed with days during which he was pyrexic, he was said to have "occasional spikes" in temperature. In addition, fever was classified as intermittent, remittent, and sustained (9).

Each febrile episode was tabulated separately, and two patients had two episodes of fever while three each had three bouts of pyrexia.

Bacterial infection was said to be present only if demonstrated by appropriate cultures; patients with negative cultures and normal urinalyses and chest X rays were considered to be free of infection.

The tumor was defined as localized in the absence of demonstrable distant metastases, or if extension was confined to regional structures. Patients with distant deposits of tumor were assumed to have metastatic disease. Patients with minor cutaneous neoplasms were not included in the analysis.

Response to antibiotics was often difficult to evaluate, but a salutary response was presumed to have occurred in patients whose temperatures returned to normal in close temporal sequence to the administration of antibiotics and in whom there was no other cause to account for defervescence.

For the purpose of analysis, the tumors were divided into four large groups (Table 1). This classification will be retained throughout the study.

RESULTS

CAUSAL RELATION OF CANCER TO FEVER

Among 343 patients 102 had no fever, while 241 had 249 bouts of pyrexia (Table 2). Each of these febrile episodes was evaluated for its relationship to the tumor. Some were felt to be *unrelated* as illustrated by a patient with carcinoma of the prostate

TABLE 2. Causal Relation of Fever to Cancer

Site	No. Fever	Fever				
		Directly due to Cancer	Indirectly Related	Unrelated	Unknown	Total
Pelvic	40 (30%)	3 (2%)	67 (50%)	17 (12%)	8 (6%)	135
Visceral	36 (28%)	9 (7%)	45 (35%)	22 (17%)	16 (13%)	128
Miscell.	17 (30%)	1 (2%)	19 (34%)	7 (13%)	12 (21%)	56
Lymphoma	9 (28%)	6 (19%)	1 (3%)	11 (34%)	5 (16%)	32
Total	102	19	132	57	41	351
%	29.1	5.4	37.6	16.2	11.7	100

who was admitted because of pneumococcal pneumonia. Many episodes were the result of obstruction or infection produced by the tumor or followed in the wake of surgery aimed at its removal; these were defined as *indirectly related*. In the absence of these features, fever was felt to be *directly related* to the neoplastic process provided sufficient data were available to eliminate other causes of fever. In some instances, no study to clarify the cause of fever had been performed and these cases were placed in a special category designated *unknown*.

Regardless of site of origin, approximately 30% of patients remained afebrile. Only 2% of febrile episodes were directly due to neoplasm in the pelvis, breast, brain, and face. The incidence of fever directly due to visceral and lymphatic carcinoma (7% and 19%) was considerably higher. The most common causes of fever in neoplasia were obstruction, infection, and postoperative complications. This was particularly true in carcinomas involving the genitourinary structures. *Indirectly related* fevers were singularly uncommon in patients with lymphomas, sarcomas, and multiple myelomas. On the other hand, 34% of these patients had fever thought to be unrelated to tumors. For the most part these were episodes of pneumococcal pneumonia and Gram-negative sepsis, both of which are common in patients with alterations in host resistance. In the remainder of the groups approximately 15% of febrile episodes were unrelated to the malignant process.

Table 3 correlates the cause of fever with the extent of the neoplastic process. There were as many afebrile patients among those with metastatic disease as among those whose tumor remained confined to its locus of origin. On the other hand, there were four times as many patients with disseminated cancer who had fever due to the tumor *per se*, as among those with localized disease. This was true even when patients with lymphoma and sarcoma were removed from the group with disseminated malignancy. Conversely, more patients had fever indirectly related to cancer when the neoplasm had remained localized.

In Table 4 the cause of fever is analyzed with respect to the site of the tumor and presence of metastatic disease. Lymphomas and sarcomas have been excluded since all were assumed to have metastasized widely. Afebrile patients were equally distributed among all groups regardless of origin or dissemination. Among localized tumors, only those arising in the abdomen or chest were directly responsible for fever. The propensity for cancer originating in the pelvis to produce fever by means of secondary obstruction and infection again stands out. Distant spread did not increase the incidence of fever in this group.

HEIGHT AND DURATION OF FEVER

The height and duration of fever in each diagnostic category are illustrated in Figure 1. These values are at best an approximation and are subject to a number of uncontrolled variables including fever prior

TABLE 3. Relationship of Extent to Cancer of Cause of Fever

	None	Direct	Indirect	Unrelated	Unknown	Total
Local						
(No.)	52	4	84	34	21	195
(%)	26.7	2.0	43.1	17.4	10.8	100
Metastatic						
(No.)	50	15	58	23	20	156
(%)	32.1	9.6	30.8	15.0	12.8	100

TABLE 4. Causal Relation of Fever to Site and Extent of Cancer

Site		No Fever	Fever due to Carcinoma	Fever Indirectly Related	Unrelated	Unknown
Pelvic	Loc.*	30 (28.3)§	0	54 (50.9)	17 (16.1)	5 (4.7)
	Met.†	10 (34.5)	3 (10.3)	13 (44.9)	0	3 (10.3)
Visceral	Loc.*	11 (23.4)	4 (8.5)	15 (31.9)	11 (23.4)	6 (12.8)
	Met.†	25 (30.9)	5 (6.1)	30 (37.1)	11 (13.6)	10 (12.3)
Miscell.‡	Loc.*	11 (26.2)	0	15 (35.7)	6 (4.3)	10 (23.8)
	Met.†	6 (43.2)	1 (7.3)	4 (28.8)	1 (7.3)	2 (14.4)

* Local.
† Metastatic.
‡ All cases of metastatic cancer in miscellaneous group had carcinoma of breast.
§ ( ) = %.

to admission, antipyretic and antimicrobial therapy, death during hospitalization, surgical procedures, and so forth. Nevertheless, it can be seen that there was little difference in the magnitude and duration of fever except that pyrexia attributed directly to cancer persisted for a much longer period than fever indirectly related or unrelated to malignancy. This is not surprising since these patients' fever was by definition more difficult to diagnose and was less amenable to treatment.

Table 5 describes in detail the duration and height of fever in patients whose elevated temperature was thought to be due to carcinoma. There were 19 bouts of pyrexia among 18 patients. All but four of these tumors were widely disseminated; the others had invaded regional structures. Exclusive of leukemias, nine of 16 tumors had spread to the liver. In most instances the fever was remittent and ranged between 101 and 104 F.

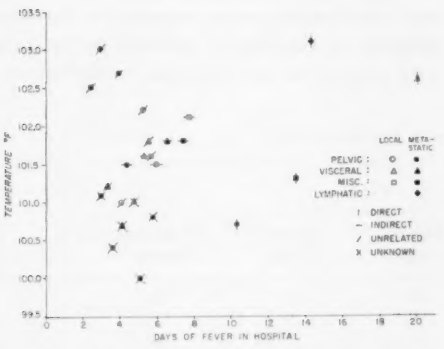

FIGURE 1. Duration and height of fever in patients with various types of malignancy.

FEVER INDIRECTLY RELATED TO CANCER

Forty-nine instances of fever in patients with cancer were complications following measures directed at therapy of the tumor including endoscopies, biopsies, radiation and nitrogen mustard therapy, and operations. These complications included development of abscesses, wound dehiscence, atelectasis, and thrombophlebitis. Seven febrile episodes followed transurethral resections, and an additional 20 patients developed urinary tract infection after insertion of Foley catheters.

Obstruction with and without infection accounted for fever in 43 patients. Twenty-two had obstruction of urinary flow, and bronchostenosis produced by pulmonary neoplasms was associated with fever in 19 instances. Blockage of the biliary tract and

TABLE 5. Extent and Type of Fever Directly Related to Cancer

Primary Site	Metastatic Site	Degrees F	Fever Days	Type
Pelvic				
Cervix	Lung, bone	100	10	—
Prostate	Lung, bone	100	3	—
Ovary	Liver, peritoneum	101.2	18	R*
Visceral				
Lung	Pleura	101.6	51	R*
Stomach	Liver	101	3	I†
Rectosigmoid	Nodes	101	11	R*
Pancreas	Peritoneum, liver	102	46	R*
Pancreas	Peritoneum, liver	102	2	OS‡
Pancreas	Nodes	102.4	14	I†
Bile duct	None	100	4	I†
Unknown	Liver	102.6	16	R*
Unknown	Liver	104	16	R*
Miscellaneous				
Breast	Liver, brain	100	8	R*
Lymphoma				
Retroperitoneal sarcoma	Local extension	101	25	R*
Osteogenic sarcoma	Liver	102	15	R*
Fibrosarcoma	Liver	102.6	19	R*
Granulocytic leukemia		105	30	R*
Granulocytic leukemia		105	12	R*
Lymphatic leukemia	Lungs	101	3	R*

* Remittent.
† Intermittent.
‡ Occasional spike.

of a sinus tract accounted for other causes of obstruction.

Other complications related to cancer included four intra-abdominal fistulae, three bronchopleural fistulae, and three cutaneous infections following invasion by tumor. Two patients developed thrombophlebitis secondary to infiltration by tumor.

The causes of fever indirectly related to cancer are summarized in Table 6. The importance of urinary sepsis in pelvic malignancies cannot be emphasized too strongly. On the other hand, obstruction and fistulization were responsible for the majority of the febrile episodes in patients with abdominal and thoracic malignancies.

TABLE 6. Indirect Causes of Fever in Cancer

	Per Cent			
	Urinary Tract Infection	Wound Infection	Postop. Fever	Structural Change
Pelvic (67)*	53	9	33	5
Visceral (45)	0	5	38	57
Miscell. (12)	0	33	33	34

* ( ) = Number of cases.

Approximately one-third of patients had fever for several days after surgery. In most instances this was probably due to infection, but cultural confirmation was lacking.

FEVER UNRELATED TO CANCER

Respiratory infections were the presumed cause of fever in 24 patients. Two patients with leukemia had a peritonsillar abscess, and one patient with multiple myeloma had pneumococcal pneumonia. Of six cases with bacteremia, three occurred in patients with leukemia or myeloma. *D. pneumoniae, E. coli,* and *Ps. aeruginosa* were the pathogens cultured from blood. The propensity for patients with multiple myeloma to acquire recurrent pneumococcal infections has been mentioned by Zinneman and Hall (10), and Shaw, Szwed, Boggs, Fahey, Frei, Morrison, and Utz (11) have pointed out that host resistance is diminished in some patients with chronic lymphatic leukemia. In a sense, therefore, systemic infections in patients with tumors of the reticuloendothelial system may be causally related to the neoplasm. This relationship has not been established in solid tumors, although certain neoplasms may be associated with secondary bacterial infections with unusual pathogens. An example of this is parasitization of carcinomas by *Salmonella* (12, 13).

Other causes for fever presumed to be unrelated to cancer included cerebral, pulmonary and myocardial infarcts in five instances, thrombophlebitis in two, drug fever in three, and a transfusion reaction in one.

EFFECT OF ANTIMICROBIALS ON FEVER

Slightly more than one-half the patients received antibiotics during the course of fever. Rather than attribute defervescence to this form of therapy, the number of patients in each group who remained febrile while receiving antibiotics was compared with those in the same group who were not treated with these agents (Table 7). Antibiotics did not affect the number of patients remaining febrile in the groups with fever directly or indirectly related to neoplasm. Although elevations in temperature were more refractory in patients with metastatic than with localized cancer, antimicrobial therapy did not reduce the ele-

TABLE 7. Effect of Antimicrobials on Fever in Patients with Malignant Disease

	No. Patients			
	Receiving Chemotherapy	Remained Febrile	Not Receiving Chemotherapy	Remained Febrile
Causal relation fever				
Direct	7	4	10	6
Indirect	59	6	35	3
Unrelated	32	5	20	7
Unknown	10	1	28	4
Extent				
Local	60	3	47	2
Metastatic	39	10	36	11
Site				
Pelvic	38	2	21	4
Visceral	42	8	44	8
Miscell.	19	3	17	1
Lymphatic	8	2	10	6

vated temperature. Similarly, there was no correlation between the origin of the tumor and persistence of fever despite antibiotic therapy. The sole exceptions were patients with lymphomas in whom the incidence of persistent pyrexia was two and one-half times greater among untreated patients than among those who had been given chemotherapy. This is probably due to the high incidence of systemic infections with specific pathogens in this group. Since these infections have been classified as *unrelated* to cancer, the relatively favorable response to antibiotics in this group is understandable (Table 7).

Discussion

Fever has long been recognized as a manifestation of neoplasia, and lymphomas, tumors of the kidney, lung, liver, and gastrointestinal tract have been implicated most frequently.

At the National Institutes of Health, 34 of 36 patients with acute leukemia had one or more bouts of fever during a one-year period of observation (14). Fever in sarcomas attracted attention as early as 1887, when Marsh reported two cases (15). Jaffe speaks of fever in Ewing's sarcoma as being common (16).

The incidence of fever in renal carcinoma is variable. Allemann and Bayer found fever in five of 38 cases (17), Soloway in eight of 130 patients (5), Young in four of 43 (18), and Castano in three of six (19). Fedoroff reported an incidence of 25% (20).

There is even more variation in the reported incidence of fever among patients with carcinoma of the lung. For example, Ochsner, DeBakey, and Dixon report no fever among 129 patients (21). Rienhoff noted an incidence of 13% (22), while pyrexia occurred in 50% of Stivelman's patients (23). Bloomer and Lindskog stated that 23 of 100 patients with carcinoma had pulmonary infection; these were the only febrile patients (24).

In the first edition of Osler and McCrae's textbook of medicine (25), fever was described in 74 of 150 patients with carcinoma of the stomach. In 1914 Friedenwald reported an incidence of pyrexia in 43% of 1,000 patients with gastric carcinoma (26). A similar figure for incidence was cited by Briggs in 1923 (27). As recently as 1950 one author stated that only 15% of 69 patients with gastric neoplasms were admitted to hospital afebrile (28).

The incidence of fever in other neoplasms is also reported to be high. For example, fever was present in 21% of cases of esophageal and pharyngeal cancer (29), in 70% of colonic carcinoma (30), and in 45% and 61% in two series of biliary tract malignancies (27, 29). Interestingly enough, a recent report gives an incidence of only 2% for fever in patients with carcinoma of the body and tail of the pancreas, but pyrexia increased in patients with carcinoma of the ampulla of Vater (31).

With a few exceptions, these figures are uniform in ascribing a high incidence of fever to cancer. The summary in Boggs' paper (8), representing a composite of cases culled from the literature, emphasizes that fever in cancer *in the absence of infection* is very common indeed.

Our data are in agreement with the fact that 70% of patients with cancer have fever, but they strongly suggest that infection or localized obstruction produced by the tumor is responsible for the fever in the majority of patients and that fever due to cancer *per se* is exceedingly rare.

These results are somewhat at variance with those of Boggs and Frei (8) who analyzed 127 cases of malignancy and found fever to be unrelated to infection in 56%. Our data, based upon 351 cases, show that fever was directly due to cancer in only 5.4% but was a consequence of infection or obstruction produced by cancer in 37.6% cases. Among our patients 16.2% had fever ascribed to infection or destruction of tissue which was felt to be unrelated to

the neoplasm. Finally, in 11.7% of our patients insufficient information was available to determine the cause of fever.

Actually, the differences between our data and Boggs' are more apparent than real. Most of his patients had lymphomas or leukemia; in these the incidence of fever unassociated with infection is notoriously high (14). Although very few of our patients had this type of neoplasm, the incidence of fever among them was also greater than among those with solid tumors. Furthermore, the criteria used to establish the etiologic relationship between fever and cancer in the two studies differed considerably. Patients with systemic infections who were felt to have fever unrelated to cancer in our study would have been placed in the "fever due to infection" group in Boggs' series, and the patients with obstructive carcinoma, whose fever was thought to be indirectly related to neoplasm by us, would have been grouped by Boggs and Frei with those whose fever was directly attributable to cancer. Finally, Boggs' and Frei's patients were available for prolonged periods of observation, making their data more definitive, and it seems conceivable that our results would have been different had we been able to observe our patients for a longer period.

From a practical point of view, however, these observations have some value, for they clearly delineate the common causes of fever in certain types of malignancies. The febrile patient with cancer of the prostate, bladder, cervix, or uterus most likely has a urinary tract infection as the basis for fever; in the patient with cancer of the lung, bronchostenosis with distal infection is most often the culprit; and in abdominal carcinomatosis obstruction of the bowel or fistula formation should be suspected as the cause of pyrexia. In patients with reticuloendothelial tumors, a systemic infection caused by a specific pathogen, such as the pneumococcus, the staphylococcus, *E. coli*, or *Pseudomonas* is the most likely reason for fever. Until these possibilities have been ruled out by the appropriate bacteriologic, radiographic, and endoscopic methods, extensive study of these patients for fever of undetermined origin does not seem warranted.

In the majority of the patients spontaneous defervescence occurred, and except in patients with lymphomas with specific infections which responded well to antimicrobial therapy, antibiotics did not exert an appreciable influence on the fever. This might be used as an argument against the hypothesis that most of these fevers were causally related to infection. When it is considered, however, that the majority of infections were related to obstruction or the presence of a foreign body, most often a urethral catheter or a suture, lysis of fever following removal of these obstacles is not surprising. Furthermore, a great many fevers were the result of urinary tract infections in which spontaneous disappearance of fever is the rule.

The mechanism of fever in patients with cancer without overt obstruction or infection has been the subject of much speculation. Ulceration of normal or malignant tissue has been incriminated in the pathogenesis of fever in carcinomas involving the gastrointestinal tract. Berlin and Porter found that two of 12 afebrile patients admitted with cancer of the stomach had ulcers, while eight of 11 febrile patients with gastric carcinoma had ulcers (28). A larger series of cases with careful radiologic and morphologic examination of the gastric mucosa is needed before this fact can be established.

Necrosis of tissue in a rapidly growing tumor has been thought to be related to production of fever. If this be the case, it must be a sporadic occurrence. Creevy, for example, reported two patients with hypernephroma and marked fever in whom necrosis was entirely absent and found several others, in whom there was a marked destruction of neoplastic tissue, who re-

mained afebrile (32). Experimentally, infarcted tissues from normal rabbits have not been found to be pyrogenic (33).

Whether patients with hepatic metastases are more prone to develop fever is problematical. Briggs described fever in 43 of 98 patients with primary neoplasms of the liver and gall bladder (27). Fenster and Klatskin observed fever to be unrelated to infection in 23% of 81 cases with cancer metastatic to the liver (34). In the present study 46 patients had hepatic metastases, and in six of these fever was attributable directly to tumor—an incidence of 13%, some two and one-half times that found in the entire group. The possibility that fever among patients with hepatic metastases is due to failure of conjugation of etiocholanolone with glucuronic acid should be considered (35), since it has been shown that free etiocholanolone is pyrogenic for man (36). Similarly, the endogenous biliary steroid, lithocholic acid, has significant pyrogenic action for man (37). It is conceivable that tumor in the liver interferes in some unknown fashion with degradation of cholesterol to bile acids resulting in an excess of this pyrogenic compound in the circulation. Both of these possibilities deserve careful study.

Finally, infiltration of the tumor by leukocytes may be important in the pathogenesis of fever in cancer. We have recently observed a patient with a hepatoma metastatic to the skin who had marked intermittent fever (38). Removal of this metastatic focus was followed by prompt defervescence, and careful cultures of the tumor as well as blood failed to reveal pathogenic microorganisms. Histologically, the tumor was densely infiltrated with polymorphonuclear leukocytes. Of many cell types examined, the granulocyte is the only one pyrogenic for experimental animals and is the presumed source of the circulating endogenous pyrogen found in many types of experimental fever (39). It is conceivable that the high concentration of leukocytes in this particular tumor led to the release of endogenous pyrogen and fever. More careful examination of neoplastic tissue for infiltration with leukocytes and correlation of this phenomenon with fever may be of value.

Summary and Conclusions

Three hundred fifty-one episodes of fever in 343 patients with malignant disease admitted to King County Hospital were examined to determine the cause of fever, its height and duration, and its clinical significance. Thirty per cent had no elevation in temperature, in 38% fever was due to infection or obstruction, in 16% pyrexia was felt to be unrelated to the tumor, and in only 5.4% of patients was fever directly attributable to cancer. In this group lymphomas predominated, and in patients with metastatic tumors the frequency of fever was four times greater than in the group in whom the neoplasm had remained localized. Urinary tract infections were responsible most often for fever in patients with pelvic neoplasms; bronchostenosis was the most common cause in carcinoma of the lung; obstruction or fistula formation occurred in abdominal patients with lymphoma, sarcoma, or leukemia who were deemed to have some aberration in host resistance. In most instances, the fever subsided spontaneously, and, except in bacteremia associated with lymphoma, administration of antibiotics did not enhance lysis of fever.

Summario in Interlingua

Tres centos cinquanta-un episodios de febre in 343 patientes con morbos maligne, admittite al Hospital King County (in Seattle, Washington) esseva examinate pro determinar le causa del febre, su altor e duration, e su signification clinic. Trenta pro cento habeva nulle augmento del temperatura; in 38% le febre esseva causate per infection o obstruction; in 16% le pyrexia esseva considerate como non relationate con le tumor; e in solmente 5,4% le febre del patiente esseva directemente attri-

buibile al cancere. In iste gruppo, lymphomas predominava, e in patientes con tumores metastatic le frequentia de febre esseva quatro vices plus grande que in le gruppo in qui le neoplasmas habeva remanite localisate. Infectiones del vias urinari esseva le causa le plus frequente de febre in patientes con neoplasmas pelvic; bronchostenosis predominava como causas de febre in carcinoma pulmonar; obstruction o formation de fistulas in cancere abdominal; e infectiones systemic pro micro-organismos specific in patientes con lymphoma, sarcoma, o leucemia in qui un aberration del resistentia contra ille organismos esseva supponite. In le majoritate del casos, le febre subsideva spontaneemente. Excepte in casos de bacteremia associate con lymphoma, le administration de antibioticos non promoveva le lyse del febre.

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Amyloidosis

MAJOR GORDON W. BRIGGS (MC), USA, *Washington, D. C.*

AMYLOIDOSIS IS A DISEASE of unknown cause characterized by the accumulation of an amorphous, proteinaceous material in various organs and tissues of the body. Rokitansky (1), in 1842, is usually credited with the first description of the disease in association with chronic sepsis. It remained for Virchow, ten years later, to attach the name amyloid. Wild, in 1886, first described a form of amyloidosis not associated with a preceding chronic disease (2).

The purpose of this paper is to report the findings in 73 autopsied cases and to review certain concepts and manifestations of amyloidosis.

The classification advanced by Reimann, Koucky, and Eklund (3) in 1935 has continued to enjoy general acceptance. Their classification was as follows:

1. Primary amyloidosis characterized by absence of preceding disease; involvement of mesodermal tissue, that is, cardiovascular system, gastrointestinal tract, smooth and striated muscle, and lymph nodes.
2. Secondary amyloidosis, the form that may follow chronic disease and is characterized by large deposits of amyloid, especially in the spleen, liver, kidneys, and adrenals.
3. Tumor-forming amyloidosis characterized by the presence of small, solitary or multiple tumors in the eye, bladder, urethra, pharynx, tongue, and especially in the respiratory tract.
4. Amyloidosis occurring with multiple myeloma.

King (4) proposed a classification based on the anatomic localization of the amyloid deposits, namely, typical amyloidosis, with deposits in the usual sites (kidneys, spleen, liver, adrenals), and atypical amyloidosis, deposits not following the usual or typical distribution but found in one or many foci or organs. King then divided the two categories of typical and atypical into two subgroups: (a) those associated with other disease, and (b) those not associated with other disease.

Many other classifications have been suggested, usually variations of those outlined (5). The following terms have been used synonymously with primary amyloidosis: idiopathic, systematized, diffuse, para-amyloidosis, atypical, primary atypical, and mesenchymatous. Synonyms for secondary amyloidosis include the terms typical, genuine, visceral, and general parenchymatous.

With the advent of antibiotics, it was believed that secondary amyloidosis had been relegated to a position of obscurity. But now it is being recognized more frequently in association with a bewildering array of diseases including rheumatoid arthritis, Hodgkin's disease, and regional enteritis (Table 1). The recognition of familial amyloidosis and the unsolved problem of the relationship of multiple myeloma (plasma cells) to amyloidosis are problems intriguing to both clinician and research worker. The clinician may well

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Requests for reprints should be addressed to Major Gordon W. Briggs (MC), USA, Gastroenterology Clinic, Walter Reed General Hospital, Washington 12, D. C.

TABLE 1. List of Diseases Associated with Secondary Amyloidosis

Paraplegia, traumatic	18
Paraplegia, secondary to:	
Transverse myelitis	2
Multiple sclerosis	2
Sarcoma, involving spinal cord	2
Tuberculosis, pulmonary	6
Tuberculosis, miliary	1
Rheumatoid arthritis	4
Hodgkin's disease	3
Bronchiectasis	3
Pyelonephritis, chronic	3
Ulcerative colitis	2
Leprosy	1
Enteritis, regional	1
Renal cell carcinoma	1
Perineal fistula	1
Tertiary syphilis	1
Empyema, gall bladder	1
Peritoneal abscess	1
Total	53

contribute considerable knowledge to these problems through studies of family groups in the first instance and diagnosis and bone marrow studies early in the course of the disease in the second instance.

The clinician's interest assumes a practical turn when it is realized that amyloidosis is a polysystemic disease that should be considered in diagnostic dilemmas concerning renal disorders, cardiac enlargement, neuropathies, bleeding tendency, and other disorders as brought out later in this paper.

Chemical Composition

Hass and Schulz (6) isolated two protein fractions from amyloid associated with tuberculosis. Hass (7) later reported that 0.5 to 1.5% of the amyloid matrix was composed of polysaccharide. It has become customary to state that amyloid is a protein in association with a polysaccharide of chondroitin-sulfuric acid type. As late as 1957, Windrum and Kramer (8), using histochemical techniques, demonstrated a polysaccharide of the chondroitin-sulfuric acid type in secondary amyloidosis. Calkins and Cohen (9), however, report that amyloid is a protein containing glucosamine, galactose, mannose, fucose, and little, if any, chondroitin sulphate. Amyloid is not a collagen product. Teilum (10) has suggested that amyloid is a series of closely related protein compounds that vary from case to case and even from area to area in the same case. He classified these compounds as glycoproteins.

Vasquez and Dixon (11) demonstrated the affinity of fluorescent-labeled antigammaglobulin serum for secondary amyloid thus suggesting a chemical relationship between amyloid and gammaglobulin. Amyloidosis can be produced in laboratory animals by such means as the injection of sodium caseinate (12), bacteria (13), sodium ribonucleate (14), albumin, gelatin (15), methylcholanthrene (16), and by feeding a diet of cheese. Hoffman, Friedfeld, Fishberg, and Fishberg (17) demonstrated amyloid deposits in cholesterol-fed rabbits. The conflicting reports on the chemical nature of amyloid may be due in part to the variability in the substances injected and the different animals used as experimental models.

Pathogenesis and Formation

There is considerable difference of opinion as to where and by what process amyloid is formed. Some years ago Mallory (18) thought that amyloid was the product of perverted fibroblastic activity. In 1927, Smetana (19) stated that amyloid was formed by the phagocytic cells of the reticuloendothelial system. More recently Teilum (10) has reported that amyloid is the result of the local production and precipitation of amyloid by reticuloendothelial cells. Reimann, Sahyoun, and Chaglassian (20) postulated that amyloidosis might be considered to be a form of proteinosis with storage of normal or abnormal protein somewhat analogous to glycogen storage in von Gierke's disease.

Perhaps the most popular hypothesis at present relates amyloid formation to an immune mechanism. The fact that horses

which are used to produce antisera frequently have amyloidosis is cited in support of that hypothesis. Such horses also have an accompanying hypergammaglobulinemia, as do other animals that develop amyloidosis from the injection of bacteria. Such factors, plus the association of hypergammaglobulinemia and amyloidosis with multiple myeloma, lead some to believe that amyloidosis is caused by the deposition of globulin or a gammaglobulin complex in various tissues. But Calkins, Cohen, and Larsen (21) were unable to confirm the globulin content of amyloid deposits. On the other hand, the work of Vasquez and Dixon (11) indicates that amyloid contains significant amounts of gammaglobulin and supports the antigen-antibody theory of origin but does not exclude the possibility that amyloid may arise by other processes.

These studies concerning the chemical composition and formation of amyloid deal chiefly with secondary amyloidosis in humans or amyloid produced in animals on an experimental basis. Osserman (22) recently postulated that in primary amyloidosis and in amyloidosis associated with multiple myeloma, proteins of low molecular weight similar to Bence Jones protein, produced by abnormal plasma cells, diffuse through capillary beds (accounting for the common subendothelial location of amyloid) and form insoluble complexes with polysaccharides which are recognized as amyloid deposits.

Pathologic Anatomy

Amyloid is an amorphous, eosinophilic material. It stains brown with iodine solution and blue or bluish-black when the iodine is followed by sulfuric acid. Metachromatic staining (amyloid red, surrounding tissue blue) is characteristic with methyl or cresyl violet dyes. Congo red imparts a characteristic pink or red color. The staining reaction of amyloid is rather variable from case to case and sometimes varies in different deposits in an individual case. Certain fluorescent dyes appear to be sensitive stains for amyloid and offer the possibility of greatly enhancing histological studies of amyloidosis (23).

In well-developed cases, amyloid imparts a firm, pale, waxy appearance to the involved tissue. Amyloid appears to be quite amorphous under the light microscope, but electron microscopy of primary, secondary, and experimental amyloid deposits has shown them to be of similar, delicate fibrillar structure (24). Larsen (25) stated that amyloid deposition occurs primarily about venocapillary endothelium from which it eventually extends into the surrounding tissue. On the other hand, Peters (26) found amyloid deposited intimately on cell membranes and suggested that this was the starting point for deposition. Amyloid is also found in direct relation to reticular fibrils (10). Whatever may be its point of origin, there is striking and generalized involvement of smaller arteries and capillaries. The involved vessels eventually become thick-walled, tubular structures with or without patent lumina (27). Progressive ischemia and compression atrophy of involved organs are evident.

Amyloid rings sometimes are formed about fat and muscle cells. Nodular and strial deposits may be seen, especially in mesenchymal tissue. In some cases these nodular deposits may become quite massive. In parenchymatous organs there often is replacement of tissue by amyloid. At other times there appears to be only vascular involvement in these organs. Seldom is there uniformity in the degree of involvement of different organs and tissues in any single case of amyloidosis.

Analysis of Case Material

Seventy-three cases of amyloidosis from the files of the Armed Forces Institute of Pathology were reviewed. All were autopsied between 1950 and 1959. Fifty-three cases were considered to represent secondary amyloidosis because there was an ac-

companying disease which was believed to have contributed to the formation of amyloidosis. The remaining 20 cases were considered to be primary amyloidosis since there was no known accompanying or preceding disease.

MANIFESTATIONS OF SECONDARY AMYLOIDOSIS

Table 1 lists the diseases which were believed to have contributed to the formation of secondary amyloidosis. Twenty-four cases were associated with paraplegia, each of which exhibited varying degrees of chronic decubitus ulcers, chronic pyelonephritis, or chronic osteomyelitis which could have contributed significantly to the development of secondary amyloidosis. Seven cases were associated with tuberculosis, six of which were of many years' duration.

Rheumatoid arthritis (four cases) followed paraplegia and tuberculosis in frequency as a precedent of amyloidosis. In a series reported by Calkins and Cohen (28), 11 (26%) of 42 cases of rheumatoid arthritis were shown to have secondary amyloidosis at autopsy. Reece and Reynolds (29) reported five cases of amyloidosis secondary to rheumatoid arthritis and cited 92 other cases reported in the literature. They did not state an incidence figure but reported that there was no apparent relationship between amyloidosis and previous therapy with gold, vaccines, or salicylates.

In the present series, amyloidosis was associated with Hodgkin's disease in three cases. Razis, Diamond, and Craver (30) reported secondary amyloidosis in five of 234 (2.1%) autopsied cases of Hodgkin's disease. Nitrogen mustard may contribute to the formation of amyloidosis (31). However, Razis et al. (30) point out that no secondary amyloidosis was found in their patients with lymphosarcoma in spite of frequent use of nitrogen mustard therapy. In 1950, Wallace, Feldman, Berlin, Harris, and Glass (32) were able to collect only 35 cases of amyloidosis secondary to Hodgkin's disease from the medical literature.

Two cases of ulcerative colitis and one case of regional enteritis were associated with amyloidosis. There was no associated extracolonic suppuration, as is often presumed, in the two cases of ulcerative colitis. The patient with regional enteritis was symptomatic for 16 years but developed suppuration in the form of a localized right lower quadrant abscess only one month before death.

Werther, Schapira, Rubinstein, and Janowitz (33) found an incidence of 29.4% (five of 17 cases) of amyloidosis in autopsies of patients dying of regional enteritis. They also were unable to relate the amyloidosis to chronic suppuration or fistula formation except, possibly, in one patient. Two of their cases died of renal failure and one of combined renal and adrenal failure secondary to amyloid involvement of these organs. The suggestion of Werther et al. (33) that amyloidosis complicates regional enteritis more often than ulcerative colitis tends to be supported by the report of Warren, Strygler, and Kobernick (34). Their patient's case was only the seventh of ulcerative colitis complicated by amyloidosis which was reported in detail and was believed to have been of only two years' duration.

Renal cell carcinoma preceded amyloidosis in one case. This is said to be the type of carcinoma most commonly associated with amyloidosis.

Fox and Morrelli (35) reported a case of periodic fever in a patient of Dutch ancestry, terminating with renal failure due to amyloidosis. This patient had had recurrent attacks of arthralgia, abdominal pain, fever, nausea, and vomiting over a 12-year period. Amyloidosis involved the kidneys, spleen, and adrenal glands. Heller, Sohar, Gafni, and Heller (36) reported that 47 of 141 patients with "familial Mediterranean fever" (periodic fever) had renal disease; 14 were proved to be due to amyloidosis,

TABLE 2. Pathologic Involvement in 53 Cases of Secondary Amyloidosis *

Organ	Cases Involved†
Liver	52/53
Spleen	51/53
Kidneys	51/53
Adrenals	49/53
Pancreas	26/48
Lymph nodes	17/32
Heart	13/52
Genitourinary system	12/45
Small bowel	11/36
Thyroid	11/34
Lungs	10/51
Stomach	7/57
Pituitary	5/27
Esophagus	4/18
Parathyroid	4/12
Large bowel	3/18
Skin	3/16
Gall bladder	2/18
Bone marrow	1/23
Muscle, skeletal	1/19

* Because of insufficient number of organs examined in many cases, this table should not be construed to represent a true frequency distribution.

† Numerator: Number of cases positive for amyloid deposits. Denominator: Number of cases in which microscopic examination of the tissue was performed.

and they believed the other cases were also due to amyloidosis.

Table 2 lists the organ involvement in the 53 cases of secondary amyoidosis. In each case involvement was recorded in accordance with the submitting pathologist. One case of miliary tuberculosis had amyloid deposits only in abdominal lymph nodes. There was involvement of the spleen, liver, kidneys, adrenals, and pancreas as commonly emphasized in secondary amyloidosis. In addition to the sites usually involved, it is to be noted that many other organs such as the thyroid, parathyroid, gastrointestinal tract, and genitourinary tract were frequently involved.

The immediate causes of death in these 53 cases were the following: renal failure, 27; bronchopneumonia, eight; one each of pulmonary embolism, pneumothorax complicating tuberculosis, and cerebral hemorrhage. In the others, the immediate cause of death was considered to be the primary disease, or was undetermined. Fifteen of the 27 cases dying from renal failure were paraplegics with associated chronic pyelonephritis, but amyloidosis was believed to play a significant part in the renal failure in each. Cohen (37) reported that five (6%) of 79 patients dying from tuberculosis complicated by amyloidosis were uremic at time of death. Thirty-seven of the 53 cases autopsied in Cohen's series (37) had shown albuminuria and renal casts during life; five had shown only albuminuria. He reported clinical hepatomegaly in 46 cases (58%), splenomegaly in 18 cases (22%), and hypertension in eight (10%) of 79 cases of secondary amyloidosis. It is generally believed that hypertension is more common in secondary than in primary amyloidosis; however, it is not common in either form of the disease.

In the present series of secondary cases, the liver was recorded as clinically enlarged in 13 (23%) and the spleen as enlarged in 11 (20%). Table 3 lists the weight distribution of the liver and spleen at autopsy. In 20 cases of secondary amyloidosis, without evidence of other types of renal disease,

TABLE 3. Weight Distribution of Liver and Spleen in 53 Patients with Secondary Amyloidosis at Autopsy

Liver weight, grams	1,900 or less (average 1,582)	1,901 to 3,000 (average 2,344)	3,001 to 4,000 (average 3,106)	4,001 or more (average 4,633)	
Number of cases	25	20	5	3	
Spleen weight, grams	200 or less (average 150)	201 to 500 (average 359)	501 to 800 (average 630)	1,000	1,650
Number of cases	19	24	8	1	1

TABLE 4. Pathologic Involvement in 20 Cases of Primary Amyloidosis *

Organ or Tissue	Total Number of Cases Involved†	Vascular Deposits Only‡
Kidney	18/20	1
Adrenal	18/20	3
Spleen	18/20	3
Liver	17/20	3
Myocardium	17/20	1
Pancreas	16/19	5
Lungs	14/20	4
Pericardium	11/18	1
Small bowel	11/15	
Genitourinary system	10/19	
Stomach	9/14	
Esophagus	9/14	
Lymph nodes	9/13	
Thyroid	8/12	3
Skeletal muscle	7/14	1
Peripheral nerves	7/9	
Bone marrow	5/13	
Aorta	5/12	
Skin	5/10	
Large bowel	5/9	
Gall bladder	5/9	1
Pituitary	4/8	1
Tongue	4/7	
Trachea: major bronchi	3/7	
Parathyroid	3/4	
Choroid plexus	2/6	
Larnyx	2/3	
Submaxillary glands	2/2	
Joints (synovia)	1/2	
Epiglottis	1/1	
Brain	0/9	

* Because of insufficient number of organs examined in many cases, this table should not be construed to represent a true frequency distribution.

† Numerator: Number of cases positive for amyloid deposits.
Denominator: Number of cases in which microscopic examination of the tissue was performed.

‡ Included in total number involved.

the kidneys weighed less than 125 grams each in five cases and exceeded 200 grams each in six cases. Thus, while the kidneys in secondary amyloidosis may be "contracted," they are more likely to be normal in size or to be enlarged.

Analysis of the symptomatology in secondary amyloidosis is unsatisfactory because of the systemic nature of the associated diseases. The presence of intermittent albuminuria eventually becoming persistent, and in some cases accompanied by urinary casts and microscopic hematuria, is usually the first manifestation of secondary amyloidosis. When these findings, especially albuminuria, develop in a patient having a disease known to precede amyloidosis, the physician should be alerted to the development of amyloidosis. The liver and spleen are or will become palpable in a number of cases. The development of amyloidosis, if recognized early, might be an indication for surgical removal of the underlying cause in such diseases as ulcerative colitis or regional enteritis.

MANIFESTATIONS OF PRIMARY AMYLOIDOSIS

Twenty of the total of 73 cases were considered to represent primary amyloidosis

because there was no significant accompanying disease. In five cases, the distribution of amyloid was that usually seen in the secondary type. There were 17 Caucasian males, one Negro male, and two Causcasian females. Rukavina et al. (15) reported the distribution as 61.6% males, 38.3% females in 154 cases; 16.8% of the males and 10.2% of the females were non-Caucasian.

The duration of the disease was ten years in one case in the present series with predominant peripheral nervous system involvement. In others, the time from onset of amyloidosis to death ranged from seven to 36 months; the average duration of symptoms was 20 months. In the present series, death occurred from age 38 to 68 years, except for one male of 81 years; excluding this case, the average age at time of death was 56 years. In Mathews' series of 50 cases (38), the average age of death was 54.8 years. Table 4 indicates that primary amyloidosis may involve any organ or system. It is truly one of the polysystemic diseases. Tables 5 and 6 list the frequency of certain symptoms and other findings in 20 cases of primary amyloidosis.

Cardiac Involvement: Amyloid deposits were present in the myocardium in 17 cases. These deposits occurred in varying degrees from case to case, in intramural vessels, as strial or nodular deposits between muscle bundles, and as rings surrounding muscle fibers. In some cases, amyloid completely replaced areas of muscle tissue. The pericardium was involved in 11 cases and the endocardium in 12 cases. Heart valves were involved in six cases and varied from microscopic to grossly visible deposits of amyloid.

TABLE 5. Symptoms in 20 Cases of Primary Amyloidosis

Symptom	Number
Dyspnea	12
Abdominal pain	7
Weakness and fatigability	7
Vomiting	6
Chest pain	5
Diarrhea	5
Diarrhea and constipation	5
Dysphagia	5
Constipation	4
Cough	4
Dry mouth	3
Paresthesia	3
Arthralgia	3
Impotence	2
Pruritus	2
Hoarseness	1

TABLE 6. Clinical Manifestations in 20 Cases of Primary Amyloidosis

Manifestation	Number
Edema	16
Enlarged liver	13
Ascites	12
Pleural effusion	9
Cardiomegaly	8
Congestive failure	8
Syncope	5
Jaundice	4
Skin lesions	4
Enlarged lymph nodes	3
Enlarged spleen	3
Murmur, systolic, cardiac	3
Enlarged tongue	2
Muscular atrophy	2
Skin rash	2
Clubbed fingers	1
Psychosis	1
Malabsorption (sprue syndrome)	1

The symptoms resulting from the cardiac involvement are difficult to determine because of the concomitant involvement of the lungs which may have led to dyspnea, renal involvement with peripheral edema and, in some cases, hepatomegaly. In addition, this older age group often had accompanying arteriosclerosis. Eight cases were believed to have a significant degree of congestive heart failure. The same eight cases were thought to have clinical cardiac enlargement. This impression was proven to be correct at autopsy in seven cases. However, cardiomegaly was not diagnosed clinically in all cases in which it occurred. At autopsy the weight of the heart varied from 350 to 450 grams in six cases, exceeded 450 grams in 11 cases, and was less than 350 grams in the remaining cases. Systolic murmurs were recorded in three cases. Rukavina (15) re-

ported murmurs in 27 (19%) of 69 cases. Twenty-two (44%) of the 50 cases reviewed by Mathews (38) had congestive heart failure, five simulated arteriosclerotic heart disease, and four simulated constrictive pericarditis. The others were variously misdiagnosed as myocarditis, rheumatic fever, or heart disease of unknown cause.

One patient in the present series, an 81-year-old Caucasian male, died from cardiac failure due to amyloid involvement of the myocardium; the only other involvement was found in the blood vessels of the pancreas. This type of amyloidosis predominantly involving the heart in elderly people is best classified as senile cardiac amyloidosis (39).

Electrocardiographic reports were available on 14 cases. Findings included nonspecific T-wave changes and low amplitude T and R waves. Various degrees of heart block were present in five patients and auricular fibrillation in one.

Renal Involvement: Amyloid was deposited chiefly in the glomeruli but also was found in the media of renal arterioles and as extravascular deposits. The renal lesions of primary and secondary amyloidosis were similar in distribution. Seven cases could be classified as the nephrotic syndrome on the basis of albuminuria, edema, and hypoalbuminemia (2.5 g/100 ml or less). Four of these seven had elevated serum cholesterol, two had hematuria, and five had elevated blood urea nitrogen ranging from 50 to 134 mg/100 ml. Sixteen of the 20 cases had persistent albuminuria. All but four had fluid retention ranging from peripheral edema to anasarca. Hematuria ranging from 6 to 100 erythrocytes per high power field was a persistent finding in five cases. Persistent hyposthenuria was a rather constant finding in the majority of cases.

Mathews (38) believed nine of 50 cases had the nephrotic syndrome. The highest blood pressure recorded in the present primary cases was 150 systolic and 92 diastolic. Mathews reported that 20% in his series had hypertension (greater than 140/90). Barclay, Cameron, and Longbridge (40), in their report, re-emphasized the feature of renal vein thrombosis in renal amyloidosis. The most common manifestation was sudden onset and rapid progression of oliguria with uremia. Ostertag (41), in 1950, described familial amyloidosis in which the predominant involvement was in the kidneys.

Gastrointestinal Involvement: Amyloid may be deposited only in the smaller blood vessels of the gastrointestinal tract. More characteristically, diffuse or nodular deposits are distributed between muscle bundles. Subserosal and mucosal deposits may also be present. Nodular deposits in the stomach, especially when accompanied by ulceration of the overlying mucosa, may be mistaken for carcinoma or peptic ulcer (42). Five patients in this series complained of dysphagia, three of dry mouth, five of diarrhea, four of constipation, and five of both diarrhea and constipation. Seven patients had abdominal pain.

Macroglossia was present in only two cases. In the 50 cases reviewed by Mathews (38), six (12%) had macroglossia. Macroglossia is often emphasized as a part of primary amyloidosis; it occurred in 33 (21.4%) of the 154 cases reviewed by Rukavina et al. (15). The tongue is large and smooth, with prominent indentations made by the teeth. Nodular protrusions may rarely be seen on the surface.

Four cases in this series were jaundiced. The cephalin cholesterol flocculation test was negative in five and did not exceed 2+ in 48 hours in any of the 11 cases in which it was recorded. The thymol turbidity exceeded 4 units in three of the ten cases in which it was performed; in those it was 5.5, 6, and 6.6 units. Thirteen (65%) had enlarged livers, clinically. At autopsy the liver exceeded 1,900 grams (1,930 to 4,496 grams) in 11 cases. Mathews (38) reported liver involvement in nine (18%) with hepatomegaly in eight (15%) of 50 cases. Rukavina

(15) reported hepatomegaly in 67 subjects (43%), with 17 cases (11%) of 154 showing clinical and laboratory evidence of liver impairment.

Skin Manifestations: Amyloid is deposited in the subcutaneous connective tissue as diffuse and nodular masses. It is also found in the walls of dermal blood vessels and in subcutaneous adipose tissue; here it may be deposited as rings around individual fat cells.

Pruritus was prominent in two cases of this series. Two cases had ecchymoses and one had recurrent ecchymoses and purpura. Petechiae or purpura may occur in repeated episodes which may involve any area of the skin but which occur most frequently in the eyelids, circumoral area, side of the nose, axillae, neck, and anogenital area. The most characteristic skin lesions are translucent, shining, smooth, yellow papules or plaques, 1 millimeter to 2 centimeters in diameter. A slight erythematous halo may appear at the base of the papules. These lesions frequently occur in the same areas as those involved by petechiae. Less characteristic nodules and masses of various sizes may appear in any area of the skin. A diffuse infiltration varying from small patches to generalized involvement simulating scleroderma may occur. However, instead of being atrophic, as in scleroderma, the skin in amyloidosis is thickened (43). During 1960, a papular skin disease involving the face and neck after excessive exposure to sunlight was described as a previously unreported form of cutaneous amyloidosis (44).

Respiratory System: Histologically amyloid may involve the pulmonary blood vessels or interstitial areas, or it may be deposited only in the submucosal tissues of the trachea and bronchi.

In the present series one patient had severe hemoptysis, two had epistaxis, and four had persistent cough. Hoarseness was prominent in one patient. Dyspnea was a prominent symptom in 12 patients but six of these were believed to have had congestive cardiac failure. Nine patients had pleural effusion: four of these were among the eight with congestive failure; two were among those with the nephrotic syndrome; two others were diagnosed as having both congestive failure and the nephrotic syndrome.

Amyloid may occur as single or multiple tumorous deposits in the larynx, trachea, or bronchi, with little or no involvement of other tissues or organs. Symptoms then depend on the size and location of the amyloid tumor (45). Also, the lungs may be involved with single or multiple amyloid nodules varying from a millimeter to several centimeters in diameter. The process may be confined to pulmonary parenchyma in such cases without involving the trachea, bronchi, or other areas (46).

Bleeding Tendency: As previously mentioned, bleeding into the skin occurred in three patients and one of these patients also had hematemesis. Another patient had severe hematemesis, one had severe hemoptysis, two patients had recurrent epistaxis, two had gross rectal bleeding, and one patient showed occult blood in the stool. The bleeding episodes were not associated with demonstrable clotting defects or thrombocytopenia.

Nervous System: Many authors have described peripheral nerve involvement with amyloid but it has not been considered to be a common finding in primary amyloidosis. Two patients in this series had paresthesias of the extremities; another had paresthesia of the trunk and unequal pupils. Syncope occurred in five cases. Two patients complained of impotence early in the course of their disease. Choroid plexus and meningeal vessels are sometimes involved with amyloid deposits. The brain is seldom involved; however, van der Horst, Stam, and Wigboldus (47) believe that certain types of senile plaques of the brain contain amyloid. They also believe these plaques may be but one manifestation of

a generalized process, "congophile angiopathy," in which amyloid is deposited in the vessels of many other organs.

Eye Involvement: Recently vitreous opacities have been emphasized as a portion of the spectrum of familial primary amyloidosis. The opacities resemble cotton-wool or glass-wool sheets as viewed by the biomicroscope and are typical of amyloidosis (48). The appearance of these amyloid deposits in the center of the ocular vitreous away from any cells certainly brings up the question again of direct deposition of amyloid by cells. In this location, the amyloid is laid down on the fibers of the vitreous at a distance from cellular elements suggesting a precipitation on the fibers and not local cellular production (48).

Adrenal Involvement: The early complaint of weakness, nausea, and associated abdominal pain and diarrhea is often suggestive of adrenal cortical failure. The infrequent association of hypertension with renal failure in amyloidosis might also be due to hypoadrenalism. Though often suspected clinically, this diagnosis was not substantiated by endocrine assays in any of the primary or secondary cases of this series.

In a series of 12 cases of amyloidosis (three primary and nine secondary), Bero (49) reported substantial hypoadrenalism in two cases and possible hypoadrenalism in two others, all in the secondary form.

Familial Form: Andrade (50), in a series comprising 42 males and 22 females, described a familial form of the disease that occurs in Portugal, beginning in the second or third decade of life, lasting seven to ten years, with a high mortality rate and predominant involvement of peripheral nerves. The nervous system symptoms were predominantly hypalgesia or analgesia, particularly of the lower extremities, and paresthesias—tingling, pricking, shooting pains in variable locations over the body surface. He believed thermal sensation disappeared first, followed by that of pain, touch, and finally posture. Pain in the extremities was common as was muscular atrophy, foot drop, and anisocoria. Gastrointestinal symptoms of distension, constipation, diarrhea, and sphincter disturbances were commonly noted.

In 1953 Kantarjian and DeJong (51) described two sisters with a syndrome starting during the third decade of life. The syndrome was characterized by the following:

[1] Neurological findings with involvement of peripheral and autonomic nerves resulting in muscle weakness, muscular atrophy, absent deep reflexes, sensory disturbances, sphincter disturbances, and trophic changes of the skin. There were marked elevation of spinal fluid protein and changes in the colloidal gold curve.

[2] Gastrointestinal symptoms of anorexia, nausea, vomiting, constipation, abdominal pain, and loss of weight.

[3] Ophthalmic changes, with loss of vision, vitreous opacities, retinal exudates, progressive exophthalmus, and pupils nonreactive to light.

[4] Endocrine disorders evidenced by enlarged thyroid, low basal metabolic rate, and amenorrhea.

[5] A systolic murmur suggestive of congenital heart disease.

A similar syndrome was present in the father of the two sisters; however, since he had died many years earlier, clinical details were less complete. Autopsy examination had shown generalized primary amyloidosis in the father and one sister. The other sister remained alive at the time of the report.

Rukavina and co-workers (15) found that 29 of 66 members of one family had evidence of familial amyloidosis, 16 with clinical disease and the remainder with a peculiar serum protein electrophoretic pattern characterized by an atypical peak between the alpha-2 and beta globulin fraction or poor resolution in the alpha-2 area. Their patients presented some or all of the

TABLE 7. Laboratory Results

	No. of Cases Examined		No. of Cases
Hemoglobin	20	below 11 g/100 ml	9
White blood cell count	20	12,000/mm³ or more	9
Erythrocyte sediment. rate (Normal 0–9 mm/hr)	Male—14	20 mm/hr	9
		10–19 mm/hr	2
		9 mm/hr or less	3
	Female— 1	40 mm/hr	
Albuminuria	20		16
Urinary casts	20		10
Hematuria	20	6 cells/high power field or more	5
Serum albumin	17	3.5 g/100 ml or less	10
Serum globulin	16	3.0 g/100 ml or more	5
Total cholesterol	13	500 mg/100 ml or more	5
		250–499 mg/100 ml	1
		249 or less	7
Blood urea nitrogen	15	21 mg/100 ml or less	4
		22–40	3
		41–60	3
		61–100	2
		101 or more	3
Alkaline phosphatase	6	elevated	3
Bromsulphalein	10	elevated	7
Spinal fluid protein	2	192 mg/100 ml	
		52 mg/100 ml	

following manifestations: peripheral neuropathy, skin changes, cardiovascular insufficiency, hepatomegaly with liver dysfunction, splenomegaly, gastrointestinal symptoms, and ocular signs and symptoms, including vitreous opacities. A similar syndrome occurring sporadically also had been described (52).

Laboratory Examination: Certain laboratory findings are listed in Table 7. Most cases showed albuminuria, and urinary casts were common. Serum albumin was low in half the cases probably because of renal loss of albumin. Elevated serum globulin also occurred. The sedimentation rate was often elevated, and mild hypochromic anemia was not uncommon.

The diagnosis in the 20 cases of primary amyloidosis was established during life by liver biopsy in four, tongue biopsy in one, peripheral nerve biopsy in one, and by the Congo red test in one. The others were diagnosed by tissue section taken after death. Negative biopsies were recorded twice for the liver and once each for gingiva, tongue, and skin. Some workers find gingival biopsy to be quite useful as a means of diagnosing amyloidosis (28). In 30 cases of amyloidosis reported by Gafni and Sohar (53), of which ten were secondary to "familial Mediterranean fever," rectal biopsy was reported as diagnostic in 26. That technique possesses obvious advantages and should be particularly useful; however, rectal involvement may not occur so frequently in primary amyloidosis or in

the forms secondary to diseases other than familial Mediterranean fever. Although not used in this series, renal biopsy should yield diagnostic tissue in a high percentage of cases of amyloidosis. Conn and Sundberg (54) have reported the utility of bone marrow aspirations in the diagnosis of both primary and secondary amyloidosis.

The Congo red test was performed in six cases. It was considered as diagnostic in one case but as nonconclusive in five cases. This test has been disappointing, in general, as one might suspect from the numerous modifications and various criteria recommended in its interpretation. Tissue biopsy seems to offer a much better opportunity for early diagnosis than the Congo red test. The studies of Rukavina et al. (15), Chambers (52), and Sallmann (48) emphasize an abnormal peak between the alpha-2 and beta globulins on serum protein electrophoresis as an aid in the diagnosis of amyloidosis. The rate of removal of Evans blue dye from the blood has recently been suggested as a method of diagnosing amyloidosis (55).

Comment

In clinical circles there remains a common belief that the diagnosis of primary amyloidosis implies a particular distribution, a peculiar tinctorial reaction, and a fairly characteristic clinical picture. There is ample evidence, however, that amyloidosis without predisposing primary disease may affect any tissue or organ, and that there is overlapping of the anatomic distribution, clinical manifestations, and staining characteristics of secondary and primary amyloidosis. While in the present series the secondary form does conform to the usual concept of predominant involvement of the kidneys, adrenals, spleen, and liver, the incidence of involvement of other organs and tissues is significant, and doubtless this incidence would be greatly increased by more complete histological studies of cases autopsied in the future. These considerations render classification on the basis of tissue or organ involvement of dubious value. The differentiation of amyloidosis into primary or secondary forms on the basis of predisposing disease is not altogether satisfactory because in the individual case it cannot be determined whether the amyloidosis developed secondarily to a given disease, or independently. Likewise, in primary amyloidosis it has not been determined that it is not secondary to some unrecognized underlying disorder. Indeed, it has been suggested that primary amyloidosis is usually, if not always, secondary to multiple myeloma or plasmacytosis (22, 56). Kyle and Bayrd (57) have reviewed this concept and evaluated the bone marrows in 44 cases of primary amyloidosis. They reported that 23 showed classic myeloma, 13 showed plasma cell disease, and the remaining eight showed abnormal but not diagnostic plasma cell disorder. They state that if primary systemic amyloidosis and systemic amyloidosis associated with multiple myeloma are separate entities, they will have to be distinguished ultimately by tests more discriminating than those now available. At present, the differentiation of amyloidosis into primary and secondary types should be based on the presence or absence of a recognized predisposing cause. A more satisfactory classification will be possible only after the fundamental etiology is understood.

The following classification is believed to represent a useful tool to aid the clinician in thinking about the disorder:

1. Primary amyloidosis (with no predisposing disease):
   a. Generalized.
   b. Familial.
   c. Respiratory:
      1. Tumorous (nodular), single or multiple.
      2. Diffuse.
2. Secondary amyloidosis (with predisposing disease).
3. Senile cardiac amyloidosis.

4. Amyloidosis secondary to multiple myeloma.
5. Tumorous or localized amyloidosis, excluding respiratory.

In no way can this classification be considered original or conclusive. It does have the advantage of not furthering the existing confusion already generated by the diversity of terms used in classification. Also, it categorizes the rather recently recognized familial form by placing it under primary amyloidosis, a logical position until the etiology of amyloidosis is better understood. The relationship between tumorous or localized and generalized primary amyloidosis has not been defined. Pulmonary amyloidosis may be either tumorous or diffuse and, in either form, is probably more common than is presently suspected. Hence, quite arbitrarily, but for emphasis, the pulmonary form is separated from other tumorous forms and classified as a subgroup of primary amyloidosis.

Senile cardiac amyloidosis (primary cardiac amyloidosis) is placed in a separate category notwithstanding the involvement of blood vessels in various other organs. The age of the patients, the predominant interstitial location of the myocardial amyloid deposits, and the degree of cardiac involvement compared with that of other viscera justify this separate category.

Amyloidosis is generally believed to occur in 10 to 15% of patients with multiple myeloma. This frequent association requires a classification separate from other secondary forms. The significance of plasma cell proliferation as frequently recorded in primary amyloidosis has not been determined, nor is the relationship of the plasma cell with the amyloidosis of multiple myeloma understood. Frequent search for plasma cells in bone marrow and other biopsy tissue early in the course of primary amyloidosis may clarify this relationship. The complete understanding of the disease, amyloidosis, (more likely a group of diseases), will come with further elucidation of the biochemical, immunological, and other undefined processes through studies on the living patient early in the course of the disease.

Summary

Amyloidosis is the deposition of a homogenous, eosinophilic material in various body tissues. It is classified as secondary or primary, depending on the presence or absence of a predisposing disease. Also, senile cardiac amyloidosis, amyloidosis secondary to multiple myeloma, and tumorous amyloidosis are classified as separate forms of the disease. A familial form, recognized during the past few years, is classified under primary amyloidosis.

Certain pathological and clinical aspects of 53 cases of secondary amyloidosis and 20 cases of the primary form are presented. The secondary form may occur at any age, and its chief manifestation is the appearance of albuminuria in association with one of the diseases known to precede amyloidosis. Other prominent findings are urinary casts, and enlarged liver, spleen, and kidneys. Occasionally the kidneys may be contracted. Hypertension is uncommon.

Primary amyloidosis arises most commonly in males beyond middle age. It is notably a polysystemic disease with predominant manifestations of renal, cardiac, gastrointestinal and, in the familial form, peripheral nerve involvement. Many other tissues or organs such as mucous membranes, skin, skeletal muscle, and endocrine glands are frequently involved. Nodular or diffuse amyloidosis confined to the respiratory tract or pulmonary tissue has been reported quite frequently. At present biopsy of the appropriate tissue offers the best chance for early diagnosis.

The relationship of the various forms of amyloidosis remains unsettled, as does the exact chemical nature of amyloid, although it is known to consist of one or more proteins in combination with polysaccharides.

Summario in Interlingua

Septanta-tres autopsiate casos de amyloidosis esseva analysate, e certe conceptos e certe manifestationes del condition esseva revistate.

Un proponite classification clinic de amyloidosis distingue (1) amyloidosis primari (sin morbo predisponitori), con le subdivisiones de (a) generalisate, (b) familial, e (c) respiratori, incluse—in iste ultime—(i) tumorose (simple o multiple) e (ii) diffuse, (2) amyloidosis secundari (sin morbo predisponitori), (3) amyloidosis cardiac de senilitate, (4) amyloidosis secundari a myeloma multiple, e (5) amyloidosis tumorose (altere que respiratori).

Le precise composition chimic de amyloide non es cognoscite. Tamen, illo consiste de un o plure proteinas in combination con polysaccharidos. Le processo per que amyloide se forma es possibilemente relationate con un mechanismo immunologic. Amyloidosis primari occurre in masculos de etates medie. Illo es un morbo polysystemic, con manifestationes predominantemente renal, cardiac, gastrointestinal, e—in le forma familial—de nervo peripheric. Membranas mucose, pelle, musculo skeletic, e glandulas endocrin es frequentemente afficite. Amyloidosis nodular o diffuse, restringite al vias respiratori ha frequentemente essite reportate.

Amyloidosis secundari occurre a non importa qual etate. Le manifestation principal es albuminuria in un del numerose morbos que cognoscitemente precede amyloidosis secundari. Altere constatationes de frequente occurrentia es cylindros urinari e allargamento de hepate, splen, e ren.

Amyloidosis cardiac del senilitate occurre in 15% del patientes con myeloma multiple. In plus, proliferation plasmocytic ha frequentemente essite notate in amyloidosis primari. Iste facto pare indicar que plasmocytos ha un rolo fundamental in le formation de amyloide mesmo in casos non associate con myeloma multiple.

Biopsia del ren, hepate, medulla ossee, pelle, o mucosa es le melior methodo pro confirmar le diagnose.

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Amyloidosis in Association with Neoplastic Disease

Report of an Unusual Case and Clinicopathological Experience at Memorial Center for Cancer and Allied Diseases during Eleven Years (1948–1958)

KENT G. KIMBALL, M.D., *New York, New York*

AMYLOIDOSIS IS A DISEASE of unknown etiology characterized by deposits in various tissues of a glycoprotein material immunologically related to normal gamma globulin (1). It occurs as localized amyloidosis, generalized "primary" amyloidosis without any predisposing disease, and generalized "secondary" amyloidosis with predisposing disease (2).

Localized amyloidosis occurs in the respiratory tract, the bladder, urethra, skin, oral mucosa, and occasionally in squamous papillomas and basal cell carcinomas of the skin (2). Primary amyloidosis consists of amyloid of slightly different staining characteristics from those of the secondary variety. It involves primarily the liver, heart, and spleen, and to a lesser extent the lungs, kidneys, gastrointestinal tract, lymph nodes, skeletal muscle, marrow, adrenals, and peripheral nerves (3). By contrast, secondary amyloidosis is associated with underlying disease and involves primarily the spleen, kidneys, adrenals, liver, lymph nodes, pancreas, and gastrointestinal tract, and to a much lesser extent the heart and lungs (4). The amyloidosis associated with 10 to 14% of the cases of multiple myeloma (2, 5) is, by definition, of the secondary variety. However, its staining properties and organ distribution resemble those of primary amyloidosis (2). Furthermore, cases are reported of amyloidosis preceding clinically evident multiple myeloma by six months to three years (1).

Secondary amyloidosis has been associated historically with tuberculosis, bronchiectasis, multiple myeloma, and rheumatoid arthritis; less commonly, with osteomyelitis, chronic fistulous and sinus tracts, chronic ulcerative colitis, regional enteritis, subacute bacterial endocarditis, lymphomas and leukemia, chronic urinary tract infections, syphilis, leprosy, and chronic infections of neoplasms and of severe burns (2, 4–6). Since the advent of antibiotic treatment for infections, tuberculosis, syphilis, and chronic sepsis are found less frequently in association with amyloidosis. The most common conditions now found with this entity are multiple myeloma, rheumatoid arthritis, and infected cancer, according to Symmers (2). In their series of autopsies from The Massachusetts General Hospital from 1950 to 1954 Calkins and Cohen (5) found that the incidence of amyloidosis was 0.5% (21 : 4,000). Of their 21 cases, 52% (11 : 21) were associated with rheumatoid arthritis; 19% (4 : 21), with multiple myeloma; one each with tuberculosis, osteomyelitis, pyelonephritis, and bronchiectasis; and three cases with no predisposing disease. The incidence of malignant tumors in Dahlin's series of secondary amyloidosis (4), which encompassed 25 years at the Mayo Clinic, was 23% (7 : 30). In

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From the Department of Medicine, Memorial Center for Cancer and Allied Diseases, New York 21, New York.

Requests for reprints should be addressed to Kent G. Kimball, M.D., Cardiovascular Research Institute, University of California Medical Center, San Francisco 22, California.

TABLE 1. Relationship of Amyloidosis to Malignant Neoplastic Disease: 4,033 Autopsies at Memorial Center (1948–1958)*

	Incidence of Amyloidosis for Each Type of Neoplastic Disease	Incidence of Each Type of Neoplastic Disease in All Cases (16) of Amyloidosis Associated with Malignancy	Incidence of Each Type of Neoplastic Disease in the Total Number (4,033) of Autopsied Cases of Malignant Neoplasms
Hodgkin's disease	7/207 (3.4%)	7/16 (44%)	207/4033 (5.13%)
Lymphosarcoma	1/127 (0.8%)	1/16 (6%)	127/4033 (3.15%)
Multiple myeloma	2/34 (6%)	2/16 (12.5%)	34/4033 (0.84%)
Rectal carcinoma	1/164 (0.6%)	1/16 (6%)†	164/4033 (4.07%)
Bronchogenic carcinoma	1/244 (0.4%)	1/16 (6%)	244/4033 (6.06%)
Carcinoma of the cervix uteri	1/210 (0.5%)	1/16 (6%)	210/4033 (5.2%)
Esophageal carcinoma	1/111 (0.9%)	1/16 (6%)	111/4033 (2.75%)
Renal carcinoma	1/46 (2%)	1/16 (6%)	46/4033 (1.14%)
Submaxillary carcinoma	1/6 (17%)	1/16 (6%)	6/4033 (0.149%)
	Total amyloidosis	16/16 (100%)	16/4033 (0.4%)

* The differences between underlined figures in a given row are statistically significant.

† Another case with carcinoma of the rectum and amyloidosis also had miliary tuberculosis, a disease commonly associated with amyloidosis, and was, therefore, eliminated from the series.

Higuchi's series of amyloidosis cases, as quoted by Hyman and Leiter (7), the incidence of cancer was only 2.4% (12 : 500 cases). Thus, it appears that the occurrence of neoplastic disease in secondary amyloidosis is less common than Symmers' observations would lead one to believe.

Because of special case selection from the large population of the New York area, Memorial Center affords an unparalleled opportunity to study the relationship of neoplastic disease to other clinical entities. Accordingly, 4,158 autopsy protocols from the 11-year period 1948 through 1958 were reviewed for information concerning the incidence and relationship of amyloidosis to neoplastic disease. Approximately 3%* of these 4,158 cases had nonmalignant neoplastic or non-neoplastic disease, leaving approximately 4,033 cases with malignant neoplastic disease. An illustrative case report is presented in the Appendix.

* This figure is based on the average of the tabulated incidence of nonmalignant neoplastic and non-neoplastic cases in the total autopsies during the last five years of the 11-year period of study.

RESULTS

INCIDENCE OF AMYLOIDOSIS IN NEOPLASTIC DISEASE

Data concerning the over-all incidence of amyloidosis, the relative incidence of the several types of malignant neoplastic diseases associated with amyloidosis, and their incidence in the total autopsy series of malignant neoplasms are summarized in Table 1. There was a total of 19 cases of amyloidosis from the entire post-mortem series during the 11-year period, or an incidence of 0.46% (19 : 4,158). One of the cases whose associated neoplasm was a benign solitary leiomyoma of the ileum actually presented a picture more consistent with

that of primary amyloidosis. Another case was associated with miliary tuberculosis and no carcinoma. A third case had both rectal carcinoma and miliary tuberculosis. The remaining 16 cases of amyloidosis were associated with malignant neoplastic disease alone, an incidence of 0.4% (16 : 4,033). Calkins reviewed the incidence of amyloidosis at a general hospital (5). In 4,000 post-mortem examinations at The Massachusetts General Hospital, the incidence of amyloidosis was similar, 0.5% (21 : 4,000). Hyman and Leiter quoted Lubarsch's series of carcinoma cases in which there was a considerably higher incidence of amyloidosis, 5% (20 : 398) (7).

As shown in Table 1, Hodgkin's disease and multiple myeloma were associated with a considerable portion of the cases of amyloidosis, 44% and 12.5%, respectively. The difference between the incidence of these entities among amyloidosis cases, 44% and 12.5%, and their incidence among the cancer cases, 5.13% and 0.84% respectively, was statistically significant ($P < .00001$ and $< .011$ respectively). There was one case of submaxillary carcinoma among the amyloidosis cases, an incidence of 6% (1 : 16). The incidence of this neoplasm among the total cancer cases was 0.149% (6 : 4,033). If this difference were to persist with succeeding cases of submaxillary carcinoma, it would also be statistically significant ($P < .024$).

ORGAN INVOLVEMENT

Table 2 compares the vital data and organ incidence of amyloidosis associated with the 16 cases of neoplastic disease at Memorial Center from 1948 through 1958 with 26 cases of renal carcinoma culled from the literature (7–20), with 154 cases of primary amyloidosis quoted by Rukavina (3), and with 30 cases of secondary amyloidosis quoted by Dahlin (4). The Memorial Hospital series was further subdivided into a lymphoma group (eight cases) and a nonlymphomatous cancer group (eight cases) for purposes of further statistical analysis. The following statements can be made:

1. The ratio of sex incidence, males : females, was 1 : 3 for cases of amyloidosis with lymphomas but 1.6 : 1 for cases of primary amyloidosis (3). This difference was statistically significant ($P < .04$). There was no significant difference between the sex ratios in the other series.

2. There was a significantly higher incidence of renal amyloidosis in the total cases with neoplastic disease, 81% (13 : 16); the renal carcinoma cases, 84% (16 : 19); and the cases of secondary amyloidosis, 93% (28 : 30) than in primary amyloidosis, 47.8% (68 : 142) ($P < .005$, $< .01$, $< .025$ respectively).

3. There was a significantly lower incidence of hepatic amyloidosis in the renal carcinoma cases, 53% (10 : 19) than in either primary amyloidosis, 72.9% (81 : 111), or secondary amyloidosis, 87% (26 : 30) ($P < .05$ and $< .025$ respectively). There was also a significantly lower incidence of hepatic amyloidosis in all the cases with neoplastic disease, 56% (9 : 16) than in secondary amyloidosis, 87% (26 : 30) ($P < .05$). The incidence of hepatic amyloidosis appeared to be comparable in primary and secondary amyloidosis.

4. There was a significantly lower incidence of adrenal amyloidosis in all the cases with neoplastic disease, 50% (8 : 16), and the renal carcinoma cases, 26% (5 : 19) than in secondary amyloidosis, 93% (27 : 29) ($P < .005$ in each instance). The incidence of adrenal involvement in primary amyloidosis was not mentioned in Rukavina's series (3).

5. There was a significantly lower incidence of lymph node amyloidosis in the total number of cases with neoplastic disease, 31% (5 : 16), and the cases of primary amyloidosis, 19.7% (28 : 142) than in secondary amyloidosis, 68% (19 : 28) ($P < .05$ and $< .005$ respectively).

6. There was a significantly lower inci-

TABLE 2. Vital Data and Organ Involvement in Amyloidosis Associated with Neoplastic Diseases (Total, Lymphomatous, and Nonlymphomatous) at Memorial Center (1948–1958); with Renal Carcinoma (Review of the Literature, 1883–1959); with Primary Amyloidosis (Rukavina's Series [3]); and with Secondary Amyloidosis (Dahlin's Series [4]) *

	Cases from Memorial Center			Cases from the Literature		
	Total 16 Cases with Neoplasms	8 Cases of Lymphoma: 7 Hodgkin's & 1 Lymphosarcoma	8 Cases of Nonlymphomatous Neoplasms†	Renal Carcinoma 26 Cases from the Literature	Primary Amyloidosis Rukavina's Series	Secondary Amyloidosis Dahlin's Series
Age in years:						
Mean	52 (16/16)	44 (8/8)	59 (8/8)	54.5 (21/21)	peak 50–59 (154/154)	39 (30/30)
Range	32–69	32–58	38–69	37–84	9–101	4–70
Sex:						
Female	56% (9/16)	75% (6/8)	37.5% (3/8)	43% (9/21)	38.3% (59/154)	—
Male	44% (7/16)	25% (2/8)	62.5% (5/8)	57% (12/21)	61.6% (95/154)	—
Race:						
Caucasian	100% (16/16)	100% (8/8)	100% (8/8)	—	85.7% (132/154)	—
Negro	0	0	0	—	14.3% (22/154)	—
Duration of illness:						
First symptoms to death:						
Mean	6 yr (16/16)	8.9 yr (8/8)	3 yr (8/8)	2.1 yr (13/13)	2.2 yr (137/137)	— (25/25)
Range	6 mo–19 yr	2 yr–19 yr	6 mo–10 yr	3 mo–6 yr	1.5 mo–15 yr	12 mo–17.7 yr

* The denominators in each fraction represent the number of determinant cases in each instance. The differences between underlined figures in a given row are statistically significant. A dash indicates inadequate data for the determination of incidence.

† This category includes cases with multiple myeloma (2), rectal carcinoma (1), bronchogenic carcinoma (1), esophageal carcinoma (1), epidermoid carcinoma of the submaxillary gland (1), renal carcinoma (1), carcinoma of the cervix (1).

‡ This figure includes only cases of parenchymal splenic involvement. The author did not break down the figures for minor blood vessel involvement of the spleen; therefore, total incidence of splenic involvement was indeterminant.

TABLE 2.—(*Continued*)

	Cases from Memorial Center			Cases from the Literature		
	Total 16 Cases with Neoplasms	8 Cases of Lymphoma: 7 Hodgkin's & 1 Lymphosarcoma	8 Cases of Non-lymphomatous Neoplasms†	Renal Carcinoma 26 Cases from the Literature	Primary Amyloidosis Rukavina's Series	Secondary Amyloidosis Dahlin's Series
Organ Involvement:						
Kidney	81% (13/16)	87.5% (7/8)	75% (6/8)	84% (16/19)	47.8% (68/142)	93% (28/30)
Spleen	69% (11/16)	62.5% (5/8)	75% (6/8)	79% (15/19)	41% (46/112)‡	100% (30/30)
Liver	56% (9/16)	37.5% (3/8)	75% (6/8)	53% (10/19)	72.9% (81/111)	87% (26/30)
Adrenals	50% (8/16)	50% (4/8)	50% (4/8)	26% (5/19)	—	93% (27/29)
Lymph nodes	31% (5/16)	25% (2/8)	37.5% (3/8)	—	19.7% (28/142)	68% (19/28)
Heart	19% (3/16)	25% (2/8)	12.5% (1/8)	—	64.7% (92/142)	43% (13/30)
Gastrointestinal	12.5% (2/16)	12.5% (1/8)	12.5% (1/8)	26% (5/19)	30.9% (44/142)	56% (15/27)
Pancreas	12.5% (2/16)	12.5% (1/8)	12.5% (1/8)	5% (1/19)	—	63% (19/30)
Lung	6% (1/16)	0	12.5% (1/8)	—	30.9% (44/142)	10% (3/30)
Parathyroid	6% (1/16)	0	12.5% (1/8)	—	—	—
Peripheral nerve	6% (1/16)	0	12.5% (1/8)	—	14.7% (21/142)	0 (0/11)
Mesentery	6% (1/16)	12.5% (1/8)	0	—	—	—
Skeletal muscle	—	—	—	—	18.3% (26/142)	—
Marrow	—	—	—	—	18% (11/61)	—
Prostate	—	—	—	—	—	62% (10/16)
Thyroid	—	—	—	—	—	59% (13/22)

dence of cardiac amyloidosis in all cases with neoplastic disease, 19% (3 : 16), the cases of nonlymphomatous neoplasms, 12.5% (1 : 8), and the cases of secondary amyloidosis, 43% (13 : 30) than in primary amyloidosis, 64.7% (92 : 142) ($P < .005$, $< .01$, and $< .025$ respectively).

7. There was a significantly lower incidence of gastrointestinal amyloidosis in all the cases with neoplastic disease, 12.5% (2 : 16), and in primary amyloidosis, 30.9% (44 : 142) than in secondary amyloidosis, 56% (15 : 27) ($P < .025$ in each instance).

8. There was a significantly lower incidence of pancreatic amyloidosis in the total number of cases with neoplastic disease, 12.5% (2 : 16), the cases of lymphoma, 12.5% (1 : 8), the cases of nonlymphomatous neoplasms, 12.5% (1 : 8), and the renal carcinoma cases, 5% (1 : 19) than in secondary amyloidosis in general, 63% (19 : 30) ($P < .005$, $< .05$, $< .05$, and $< .005$ respectively). The incidence of pancreatic involvement in primary amyloidosis was not mentioned in Rukavina's series (3).

9. There was a significantly lower incidence of pulmonary amyloidosis in the total number of cases with neoplastic disease, 6% (1 : 16), and in secondary amyloidosis, 10% (3 : 30) than in primary amyloidosis, 30.9% (44 : 142) ($P < .025$ and $< .05$ respectively).

10. The slight differences in incidence of amyloid involvement of the various other organs from one group to the other were not statistically significant.

11. The mean age at death for the lymphoma-amyloid group (44 years) was lower than that for the other groups (50 to 59 years) with the exception of the secondary amyloidosis group. Whether this difference was statistically significant was not determined. In Gall and Mallory's cases of lymphomas (21), two-thirds were less than 40 years old. Therefore, the age difference may have been related to the fact that these were lymphoma cases, and not necessarily to the presence of amyloidosis with the lymphoma.

12. The mean duration of illness in the lymphoma-amyloid group was 8.9 years as opposed to three years for the nonlymphomatous cancer-amyloid group, 2.1 years for the renal carcinoma-amyloid group, and 2.18 years for the primary amyloidosis group. The mean duration of illness for Hodgkin's disease and lymphosarcoma *per se* was 3.2 years and 2.4 years, respectively, in Gall and Mallory's series (21). Whether these differences were statistically significant was not determined. The difference would suggest that, at least in lymphoma, a longer period of illness than that commonly seen may be necessary for amyloidosis to appear. However, their figures indicating shorter duration of illness may have been due wholly or in part to the fact that these were cases seen before antibiotics were in general use. Furthermore, amyloidosis can appear in less time than is commonly thought (7). One case in the present series had renal carcinoma associated with hepatic amyloidosis at post-mortem, and had had a liver biopsy which was negative for amyloidosis only one year prior to death.

SIGNS, SYMPTOMS, AND LABORATORY ABNORMALITIES

Table 3 summarizes the incidence of signs, symptoms, and laboratory abnormalities for the same six groups previously discussed. The following conclusions can be drawn:

1. There was a higher incidence of fever in amyloidosis cases associated with cancer, 72 to 100%, than there was in primary amyloidosis, 1.3%. These differences were highly significant ($P < 10^{-7}$ for each of the three neoplastic disease categories compared with primary amyloidosis).

2. Anemia was seen in 100% of the determinant cases of amyloidosis associated with neoplastic disease. The incidence of anemia was not analyzed in Rukavina's or Dahlin's series (3, 4).

3. There was a significantly higher incidence of splenomegaly in the total cases

TABLE 3. Signs, Symptoms, and Laboratory Findings in Amyloidosis Associated with Neoplastic Disease (Total, Lymphomatous, and Nonlymphomatous) at Memorial Center (1948–1958); with Renal Carcinoma (Review of the Literature, 1883–1959); with Primary Amyloidosis (Rukavina's Series [3]); and with Secondary Amyloidosis (Dahlin's Series [4])*

	Cases from Memorial Center			Cases from the Literature		
	Total 16 Cases with Neoplasms	8 Cases of Lymphoma: 7 Hodgkin's & 1 Lymphosarcoma	8 Cases of Nonlymphomatous Neoplasms	Renal Carcinoma 26 Cases from the Literature	Primary Amyloidosis Rukavina's Series	Secondary Amyloidosis Dahlin's Series
General:						
Fever	80% (12/51)	100% (8/8)	72% (5/7)	—	1.3% (2/154)	—
Anemia	100% (15/15)	100% (7/7)	100% (8/8)	—	—	—
Renal:						
Elevated BUN† or NPN‡	73% (11/15)	57% (4/7)	87.5% (7/8)	71% (5/7)	69.7% (48/69)	— (common)
Proteinuria (3+ or greater)	36% (5/14)	67% (4/6)	12.5% (1/8)	—	44.7% (42/94)	62% (16/26)
Hypoproteinemia (<6.5 g/100 ml)	93% (13/14)	86% (6/7)	100% (7/7)	—	(<6 g/100 ml) 61.8% (29/47)	—
Edema	62% (10/16)	75% (6/8)	50% (4/8)	—	47.5% (69/145)	37% (11/30)
Nephrosis—definite	15% (2/13)	14% (1/7)	17% (1/6)	—	—	13% (4/30)
Nephrosis—definite + probable	46% (6/13)	57% (4/7)	33% (2/6)	—	—	—
Renal vein thrombosis:						
Tumor + nontumor	12.5% (2/16)	0	25% (2/8)	50% (5/10)	—	—
Tumor alone	6.25% (1/16)	0	12.5% (1/8)	40% (4/10)	—	—
Bence Jones proteinuria	—	—	—	—	0 (0/15)	—
Spleen:						
Palpable	47% (7/15)	75% (6/8)	14% (1/7)	—	13.6% (21/154)	0 (0/30)
Cardiovascular:						
Elevated blood pressure	13.3% (2/15)	0	25% (2/8)	—	28.8% (34/118)	10% (3/30)
Enlarged heart	—	—	—	—	— (86.9%)	—
Abnormal EKG§	—	—	—	—	—	—
Congestive heart failure	—	—	—	—	44.8% (69/154)	—

* The denominators in each fraction represent the number of determinant cases in each instance. The differences between underlined figures in a given row are statistically significant. A dash indicates inadequate data for the determination of incidence.

† Blood urea nitrogen.

‡ Nonprotein nitrogen.

§ Electrocardiogram.

TABLE 3.—(*Continued*)

	Cases from Memorial Center			Cases from the Literature		
	Total 16 Cases with Neoplasms	8 Cases of Lymphoma: 7 Hodgkin's & 1 Lymphosarcoma	8 Cases of Nonlymphomatous Neoplasms	Renal Carcinoma 26 Cases from the Literature	Primary Amyloidosis Rukavina's Series	Secondary Amyloidosis Dahlin's Series
Hepatic:						
Elevated alkaline phosphatase (> 3.5 Bodansky units)	55% (6/11) (3.6–24.9 B.U.)	80% (4/5) (6.4–24.9 B.U.)	33% (2/6) (3.6–11.2 B.U.)	—	— (10.5–36.5 B.U. in 3/5)	— —
Elevated bilirubin (>1 mg/100 ml)	25% (2/8) (7.3–20.6 mg/100 ml)	40% (2/5) (7.3–20.6 mg/100 ml)	0	—	37.5% (6/16) (2.0–16.3 mg/100 ml)	—
Elevated cholesterol (>260 mg/100 ml)	29% (2/7) (300 & 313 mg/100 ml)	40% (2/5) (300 & 313 mg/100 ml)	0	—	—	— (405–946 mg/100 ml in 5/8)
Elevated thymol turbidity (>1.7 units)	12.5% (1/8) (10.5 units)	25% (1/4) (10.5 units)	0	—	— (abnormal in 2 cases)	—
Elevated cephalin flocculation (2+ or greater)	40% (4/10)	33% (2/6)	50% (2/4)	—	14% (1/7)	—
Elevated BSP retention‖ (>5% after 45′)	100% (5/5) (19–23%)	100% (3/3) (21–23%)	100% (2/2) (19–21%)	—	— (21–41% in 6 cases)	100% (1/1)
Elevated prothrombin time (>17 sec. at Memorial Center)	57% (4/7) (18.6–19.2″)	50% (1/2) (19.1″)	60% (3/5) (18.6–19.2″)		43.7% (7/16)	—
Abnormal serum electrophoresis	—	—	—	—	83% (29/35)	—
Enlarged liver	—	—	—	—	43.5% (67/154)	10% (3/30)
Gastrointestinal:						
Significant diarrhea	64% (9/14)	71% (5/7)	57% (4/7)	71% (5/7)	14.9% (diarrhea or bloody stools)	—
Malabsorption	15% (1/7)	33% (1/3)	0	—	—	—
Pancreatic:						
Elevated serum amylase	50% (1/2)	50% (1/2)	—	—	—	—

‖ Bromsulphalein.

with neoplastic disease, 47% (7 : 15), and lymphoma group, 75% (6 : 8), but a significantly lower incidence of splenomegaly in the group with secondary amyloidosis, 0% (0 : 30) than in primary amyloidosis, 13.6% (21 : 154) ($P < .002$, $< .00015$, $< .015$ respectively). The high incidence of splenomegaly in the cancer group appeared to be due to the high incidence of lymphoma cases, most of which had splenomegaly, in contrast to those with nonlymphomatous malignancy.

4. There was a slight but significantly lower incidence of hypertension in secondary amyloidosis, 10% (3 : 30) than in primary amyloidosis, 28.8% (34 : 118) ($P < .017$). This may have been related to age, however, since the mean age of the secondary amyloidosis group was considerably lower than that of the primary amyloidosis group.

5. There was also a slight but significantly lower incidence of hepatomegaly in secondary amyloidosis, 10% (3 : 30) than in primary amyloidosis, 43.5% (67 : 154) ($P < .0001$) in spite of the fact that both groups had a comparably high incidence of hepatic amyloidosis (72.9% and 87% respectively).

6. The differences in incidence of other phenomena in each of the groups (Table 3) were not statistically significant. Of interest, however, was the high incidence of elevated blood urea nitrogen, hypoproteinemia, and edema in all groups, and significant diarrhea in the cancer group.

Discussion

Regarding the case to be presented, the patient was in the upper age range of cases of cancer and amyloidosis (68 years). The duration of her illness was indeterminant since the tumor of the left kidney was occult and it was impossible to state when the onset of amyloidosis occurred. It was probably well under way one year prior to her death when weight loss began.

The organ distribution of the patient's amyloidosis (kidney, spleen, liver, adrenals) followed that expected for secondary amyloidosis and amyloidosis associated with neoplastic disease. It was somewhat atypical in that it also involved the heart, gastrointestinal tract, and pancreas.

Renal Abnormalities

The renal abnormalities were typical of those seen in cancer-amyloidosis cases with a high terminal blood urea nitrogen, hypoproteinemia, edema, and, as in some cases, a nephrotic picture. Although striking qualitative proteinuria was not noted, as in other nonlymphomatous cancer-amyloidosis cases, the patient had total 24-hour proteinuria in the 4 to 12 gram range. Furthermore, except for the absence of an elevated serum cholesterol and doubly refractile fat bodies in the urine, the patient had several salient features of the nephrotic syndrome. This syndrome was seen in 46% (6 : 13) of the cancer cases with amyloidosis and 33% (2 : 6) of the nonlymphomatous cancer patients with amyloidosis. This incidence of nephrosis is similar in range to that seen in secondary amyloidosis in general, 50% (14 : 28) in Calkin's series (5). The presence of renal amyloid was undoubtedly responsible for the nephrosis and contributed significantly to the downhill course. However, this intractable course was probably accelerated by the presence of the renal vein thrombosis.* The patient's chronic diarrhea

* In the Memorial Center series, there were two instances of renal vein thrombosis associated with the amyloid-cancer cases, 12.5% (2 : 16). This was a significantly higher incidence ($P < 0.007$) than in the total cancer autopsy series, 0.79% (32 : 4,033). One of these cases had a renal tumor thrombus at the renal vein remnant after a nephrectomy for carcinoma performed one year previously. The other case had carcinoma of the cervix with widespread pelvic metastases and ascending pyelonephritis in the kidney involved by the thrombosed renal vein. Thrombosis of a renal vein *without* amyloidosis was seen in 32 cancer cases at postmortem from 1948 through 1958 at Memorial Center. The types of carcinoma associated with these 32 cases were as follows: breast, 4; cervix, 4; vulva, 3; renal, 3 (one of these also had a second primary

probably led to unrecognized dehydration which may have helped precipitate the renal vein thrombosis. The massive diarrhea of epidemic ileocolitis is a common cause of renal vein thrombosis in children (22, 23). O'Beirn (22) listed the common causes of this event in adults as follows: inflammation of the renal pedicle, ascending venous thrombosis from the lower limbs and pelvis, compression by neighboring tumors, chronic glomerulonephritis, amyloid disease of the kidneys, pyelonephritis, and eclampsia.

It is an aphorism that one should suspect amyloidosis of the kidney when there is an elevated blood urea nitrogen and a normal blood pressure. This certainly was the case with our patient. However, 13 to 25% of cases of amyloidosis associated with neoplastic disease from Memorial Center and 1.5 to 35% of cases of general amyloidosis from the literature had elevated blood pressures (24). Zuckerbrod (24) has pointed out that whenever a disease exists that might cause amyloidosis, the finding of proteinuria implies the presence of amyloidosis, and this diagnosis is not excluded by the presence of either azotemia or hypertension.

Another interesting feature in our patient was the finding of Bence Jones proteinuria. As Osserman (1) pointed out, abnormal proteins of the Bence Jones type are seen in dysproteinemias and paramyloidosis which may in turn be forerunners of multiple myeloma. Bence Jones proteinuria has also been reported in renal and gastric carcinoma, leukemia, and cancer with skeletal metastases (25). Shaw (25) reported a case of renal carcinoma, without any amyloidosis, yet with Bence Jones proteinuria, hyperglobulinemia, anemia, slight renal failure, 8.3% plasma cells in the marrow, hypoalbuminemia, and increased gamma and alpha-2 globulins. The resemblance of this case to ours is striking.

The patient's renal neoplasm was occult and occurred in a kidney that had been damaged by hydronephrosis secondary to repeated strictures associated with repeated ureterocutaneous and enteric fistulas ten years prior to death. This raises the question of the possible etiologic relationship between chronic renal damage and renal neoplasms.

Given a known and not occult renal neoplasm, how does one suspect coincident amyloidosis? Hyman and Leiter (7) mentioned the following clues: the presence of amyloidosis in the excised neoplastic kidney, evidence of unilateral renal tumor associated with azotemia, normal retrograde pyelography in the nontumorous kidney associated with poor renal function tests. These authors felt that if the diagnosis of coincidental amyloidosis with renal carcinoma was established, surgery should not be performed, as renal insufficiency would, inevitably, cause death. However, in reviewing the reported cases of renal parenchymal carcinoma associated with amyloidosis (7–20) we found 13 determinant cases (treated and untreated) with an overall five-year survival rate of 23% (3 : 13). The five-year survival rate of uncomplicated renal parenchymal carcinoma (treated cases) was reported by Nathanson (26) to be between 19 and 33%. Thus it would appear that the presence of amyloidosis should not be a deterrent to a decision for nephrectomy for hypernephroma, when otherwise indicated. McDonald (27) pointed out that other factors such as the presence or absence of renal vein involvement with tumor, and the grade of malignancy, determine the five-year survival over a range of

in the cervix); ovary, 2; reticulum cell sarcoma, 2; and one each of vagina, Fallopian tubes, rectum, colon, lung, stomach, prostate, endocervix, mixed mesodermal carcinoma of the uterus, adrenal cortex, lymphosarcoma, Hodgkin's disease, liposarcoma of buttocks, and leukemia. Of interest was the fact that 41% (13 : 32) of these cases of renal vein thrombosis were in females with tumors of the reproductive organs. Twenty-three per cent (3 : 13) of these or 9.3% (3 : 32) of the total were cases of vulvar carcinoma, a high percentage for this rare tumor.

12.5 to 58.9%; therefore, these factors probably are more important in prognosis than the presence or absence of amyloidosis.

SPLENIC ABNORMALITIES

The patient did not have a palpable spleen as was true of the majority of amyloid-cancer cases, especially of the nonlymphomatous group, 86% (6 : 7). This was so in spite of the high incidence of amyloidosis of the spleen in this group, 75% (6 : 8).

HEPATIC ABNORMALITIES

The patient manifested the same derangement of liver function as is seen in other neoplastic diseases with amyloidosis. That is, there was a slightly elevated alkaline phosphatase and bromsulphalein retention, a border-line prothrombin time, low albumin and total protein, and normal globulins. The serum electrophoresis was similar to that seen in primary amyloidosis, i.e., decreased albumin, elevated alpha globulins, normal beta, and normal to decreased gamma globulins (28).

ADRENAL ABNORMALITIES AND HYPOTENSION

The patient vomited and had diarrhea, increased pigmentation, shock, and a decreased 24-hour urinary 17-ketosteroid excretion. This low level of steroid excretion was probably invalid because of the marked oliguria present at the time. Furthermore, the patient's malabsorption syndrome itself could have explained the gastrointestinal symptoms and increased pigmentation. Moreover, even though the adrenals were involved with amyloid, this involvement was not marked. The question whether there was adrenal insufficiency remains unresolved. The lack of response to steroids suggests that factors other than adrenal insufficiency were causing the shock. However, common causes of shock were not present; there was no significant blood volume deficit, no septicemia, and no gross evidence of congestive failure. Cope and Woodrow (29) and McCutcheon (20) described cases of adrenal amyloidosis associated with a malignant cecal argentaffinoma and a renal carcinoma, respectively. Both had symptoms similar to those of our patient which were attributed to adrenal insufficiency. However, the 24-hour steroid excretion patterns were not determined in either case.

CARDIOVASCULAR ABNORMALITIES

Our patient had an enlarged heart without hemodynamically significant murmurs, hypertension, or evidence of arteriosclerotic heart disease. The anemia was not extreme and had not been present for years. The electrocardiogram showed no arrhythmia and only a minor T wave abnormality in lead II. There was no significant elevation of venous pressure (10 milliliters saline) nor prolonged circulation time (14 seconds). In retrospect, the presence of cardiac enlargement along with these findings should have raised greater suspicion of "metabolic heart disease," and, with the other clinical findings, should have provoked consideration of the diagnosis of amyloidosis earlier. It was not until the Bence Jones proteinuria and malabsorption syndrome were evident that the diagnosis of amyloidosis was considered.

GASTROINTESTINAL ABNORMALITIES

The gastrointestinal abnormalities were the most striking of the case. There was diarrhea, which was seen in 64% of cases of cancer with amyloidosis, 71% of cases of renal carcinoma with amyloidosis, but less than 14.9% of cases of primary amyloidosis. Furthermore, the diarrhea was intractable as were the vomiting and gastrointestinal bleeding.

The feature that provided the correct ante-mortem diagnosis was malabsorption. The diagnosis was made on the basis of a flat oral glucose tolerance curve with normal intravenous glucose tolerance, a low

serum carotene [39 μg/100 ml] (29), and the disordered motility studies of the small bowel on X ray.

Golden (17) elucidated the roentgenographic findings in amyloidosis of the small bowel. The transit time of barium is slowed, and gaseous distention occurs later, when the muscularis is replaced by amyloid. This condition often simulates paralytic ileus, but, unlike the latter, does not respond to urecholine administration. Gaseous distention is the most common X-ray abnormality. There may be thickening of the mucosal folds and gut wall. Narrowing and irregularity of the lumen may be present and may simulate diseases with chronic inflammation, e.g., regional enteritis. Randall (30) reported a case of amyloidosis of the small bowel associated with multiple myeloma, in which there was intestinal obstruction without bowel kinking or necrosis but merely thickening of the wall. The patient had an enterostomy but died a day later. At post-mortem there was amyloidosis confined solely to the small bowel.

Amyloidosis is an uncommon cause of sprue syndrome. Adlersberg and Schein (19) reported 40 cases of sprue seen at The Mount Sinai Hospital in New York over a 15-year period. Of these, 36 were felt to be primary sprue and four, secondary sprue. Two of the latter, 5% (2 : 40), had amyloidosis of the small bowel. One of these had renal carcinoma and the other, Hodgkin's disease. Unfortunately, post-mortem examinations were done on only ten of the 40 cases so that it is not certain whether some of the so-called "primary sprue" cases were not, in fact, those of secondary sprue. The authors found that their secondary sprue cases, in contrast to those of "primary sprue," had a shorter course, with intractable symptoms, less striking mouth lesions, persistent anemia in the absence of bleeding phenomena, and obvious iron deficiency. Our case fitted this description except for the presence of gastrointestinal bleeding.

The Diagnosis of Amyloidosis

Amyloidosis is a condition that mimics other diffuse system diseases such as the so-called collagen diseases, syphilis, sarcoidosis, aleukemic leukemia, occult lymphomas, miliary tuberculosis, multiple myeloma, and other dysproteinemias of which amyloidosis may itself be a member. Therefore, one should consider the diagnosis of associated amyloidosis in the presence of neoplastic disease when there is evidence of diffuse system involvement. However, metastasizing neoplasms can frequently present features of multi-system involvement. The high incidence of renal and hepatosplenic involvement in amyloidosis associated with cancer should aid in the diagnosis. One should suspect associated amyloidosis on finding albuminuria, edema, hypoproteinemia (without an increase in gamma globulin but with an elevated alpha and variably elevated beta globulin), a nephrotic syndrome, and an elevated blood urea nitrogen usually without hypertension. Other helpful signs are a palpable spleen and a large liver with nondescript abnormalities of function such as an elevated bromsulphalein retention (14 to 23%), and elevated alkaline phosphatase (6.4 to 24.9 Bodansky units), usually no elevation of bilirubin, normal or low cholesterol, normal thymol turbidity, normal cephalin flocculation, and a slightly elevated prothrombin time (18.6 to 19.2 seconds, control 17 seconds). If significant diarrhea, not necessarily related to amyloidosis of the gastrointestinal tract, and malabsorption syndrome are present, as in the case presented, one can make a clear diagnosis of associated amyloidosis.

If one's suspicion is increased by the presence of a number of these clinical features, other measures then can be taken to establish the diagnosis. Calkins (5) mentioned that the Congo red test was positive (20% or less retention in the serum after 60 minutes) in 60% (9 : 15) of 15 cases of

secondary amyloidosis, excluding cases of multiple myeloma. Rukavina (3) quoted evidence that these criteria were too uncertain. Of 446 autopsied cases of secondary amyloidosis in whom a total of 649 Congo red tests were done (positive if less than 10% dye remained in the serum after one hour), there were 24.3% false negatives (probably owing to the presence of only a small amount of amyloid at the time the test was performed) and 4.2% false positives (usually owing to faulty technique). Furthermore, it is important that one take into account any dye that is bound to urinary protein in cases with a large amount of proteinuria. Therefore, the Congo red test is somewhat unreliable and difficult to evaluate.

The finding of an albumin : alpha-2 globulin ratio of less than three is helpful, according to Symmers (2).

Biopsy of the gingiva may be helpful in about 30% of cases. Biopsy of the lymph nodes, skin, peripheral nerve, larynx, and the kidney has been suggested. The kidney is a particularly good site owing to its high rate of involvement with amyloid. Apparently the risks of hemorrhage are not nearly as great as with liver biopsy (5). Rukavina (3) cited the incidence of positives from biopsy of various sites in primary amyloidosis: skin, 77% (17 : 22); liver, 100% (15 : 15); lymph nodes, 45% (5 : 11); tongue, 62.5% (5 : 8); muscle, 80% (4 : 5); and gum, 100% (3 : 3). Of course the figures for secondary amyloidosis might be expected to be different owing to different organ distribution. One must be sure that biopsies are stained with Van Gieson's stain to avoid mistaking hyalinized collagen for amyloid (2).

Simultaneous determination of the blood volume by radioiodine labeled albumin and by Evan's blue dye has recently been suggested (31). The latter is bound to amyloid and, therefore, gives an apparent blood volume greater than that found with radioiodinated serum albumin by 10% or more.

Summary

An interesting case report of amyloidosis associated with a clinically occult hypernephroma and a past history of a resected colon carcinoma has been presented. The presence of a malabsorption syndrome and Bence Jones proteinuria led to the correct ante-mortem diagnosis of amyloidosis.

Autopsy records from Memorial Center for 11 years (1948 through 1958) were reviewed for the presence of amyloidosis associated with malignant neoplasms. Of 4,033 cases of cancer, amyloidosis was found in 16, an incidence of 0.4%. This was no different from the incidence of amyloidosis in a general hospital autopsy series (5). Hodgkin's disease and multiple myeloma comprised a significantly higher percentage of the amyloidosis group than was expected from their frequency in the total autopsy series. The remaining amyloidosis cases consisted of one each of the following neoplasms: lymphosarcoma, cancer of the rectum, lung, cervix, esophagus, kidney, and submaxillary gland.

The organ involvement and clinical features of the cancer-amyloidosis cases were compared with those of primary amyloidosis (Rukavina's series) and secondary amyloidosis (Dahlin's series). The organ involvement of cancer-amyloidosis cases was *different* from primary and *similar* to secondary amyloidosis by virtue of a significantly lower incidence of cardiac and pulmonary involvement. Conversely, the cancer-amyloidosis cases were *similar* to primary and *different* from secondary amyloidosis owing to a significantly lower incidence of lymph node and gastrointestinal involvement. The cancer-amyloidosis cases further differed from secondary amyloidosis alone by a significantly lower incidence of hepatic, adrenal, and pancreatic involvement.

Clinically all groups were characterized by renal abnormalities, including elevated blood urea nitrogen, hypoproteinemia, and

edema and nondescript abnormalities in liver function. The cancer-amyloidosis group also had a high incidence of fever, anemia, significant diarrhea, and splenomegaly (the latter due to the high percentage of lymphoma cases).

The diagnosis of amyloidosis associated with neoplastic disease in light of the case reported is discussed. The following features are important: albuminuria; edema; hypoproteinemia; a nephrotic picture; an elevated blood urea nitrogen, especially in the absence of hypertension; elevated serum alpha globulin with normal gamma globulins and decreased albumin; splenomegaly, hepatomegaly with minor alterations in alkaline phosphatase, bromsulphalein, and prothrombin time; diarrhea, especially if intractable; and the malabsorption syndrome. The diagnosis can be established further by laboratory studies such as renal, gum, muscle, tongue, and skin biopsy; by simultaneous blood volumes with Evan's blue dye and radioiodinated serum albumin; and by the Congo Red test.

Appendix—Case Report

E. Z., a 68-year-old widow of Russian descent, was admitted to James Ewing Hospital on February 16, 1960, complaining of watery diarrhea of four weeks' duration.

Present Illness: In 1949, a diagnosis of adenocarcinoma (grade II Duke's B) of the sigmoid colon was made, and an anterior resection was performed. A distal colostomy was required because of an abscess from spontaneous perforation at the tumor site.

In 1950, re-anastomosis of the colon and rectum and an interval appendectomy were performed. The course was complicated by a left ureterocutaneous and ureteroenteric fistula, culminating in hydronephrosis in April, 1950, and nonfunction of the left kidney in December, 1950.

In 1954, a Fishberg test revealed poor urinary concentrating ability; in 1955, the patient first noted dyspnea and weakness on exertion.

During the year prior to the final admission the patient lost 15 pounds of weight and became anemic. Anorexia, fatigue, weakness, and dull, exertional, epigastric pain appeared four months prior to admission. Two months later, the patient began vomiting several times a day to once or twice a week. On January 6, 1960, X rays of the esophagus and of the upper gastrointestinal tract revealed no pathology.

One month prior to admission the patient developed progressive ankle edema and experienced diarrhea which was watery, occasionally bloody, foul-smelling, and occurred six to ten times a day, but which was unassociated with tenesmus, melena, or steatorrhea. She also noted crampy periumbilical pain which preceded each bowel movement and was relieved by it. Four days prior to admission, a barium enema revealed a polypoid filling defect in the region of the ileocecal valve. Sigmoidoscopy revealed the mucosa to be thickened and friable.

Past History: The patient had a history of typhus fever and scarlet fever in childhood, a hysterectomy for fibroids in 1937, and resection of a benign polyp of the transverse colon in 1954.

The family history was noncontributory.

Physical Examination: The patient's blood pressure was 135/68 mm Hg; her pulse, temperature, and respirations were normal. She was pale, weak, chronically ill, with tanning of the exposed areas and palmar creases but not of the buccal mucosa. A macular scar of an old retinal detachment in the right fundus was noted. The heart was slightly enlarged. A grade II medium pitched systolic murmur was heard over the entire precordium without radiation or thrill. The liver was percussed 15 cm in vertical dimension in the right midclavicular line and was firm, blunt edged, smooth, and nontender. Soft, mobile, tender, indistinct masses were palpated in the right lower and left upper quadrants of the abdomen. The lower extremities had 3+ pitting edema.

Laboratory Data: The patient had a hemoglobin of 8.5 g/100 ml with hypochromic, microcytic indices and a positive stool guaiac. Blood urea nitrogen was 19.2 mg/100 ml. The white blood count was 12,000/mm^3 with 78% polymorphonuclears and 4% basophils. One bone marrow examination revealed 1+ normoblastic hyperplasia with no extrinsic cells; another, slight plasmacytosis.

Urinalysis revealed a specific gravity between 1.009 and 1.015, 1 to 2+ proteinuria, 2 to 12 red blood cells, and 8 to 12 white blood cells per high power field. There were no doubly refractile fat bodies under polarized light. Twenty-four hour urinary protein excretion ranged between 3.4 and 12.8 g, but stool contamination could not be ruled out. The urine was positive

for Bence Jones protein on the one occasion it was tested. A "clean catch" urine culture grew out *Proteus, Escherichia coli,* and an *Aerobacter aerogenes,* all of which were sensitive to chloromycetin. Serum electrophoresis fractionated into decreased albumin, elevated alpha-1 and alpha-2 globulins, and normal gamma globulin. Serum tested by the Korngold immunochemical method was negative for myeloma protein.

Chemical examinations of the serum revealed the following: alkaline phosphatase, 9.2 Bodansky units; calcium, 8.5 to 9.3 mg/100 ml; phosphate, 4 to 6.1 mg/100 ml; cholesterol, 130 mg/100 ml with normal ratio of esters; total protein, albumin : globulin, 3.0 : 1.7 to 3.2 : 1.9 gm/100 ml; prothrombin time, 17.8 seconds (control, 15 to 17 seconds); serum carotene, 39 μg/100 ml; a flat oral glucose tolerance test; and a normal intravenous glucose tolerance test.

Chest X ray demonstrated an enlarged heart. A skeletal survey showed osteoarthritis of the cervical and lumbar spines and a bone island in the right ilium, but no lytic lesions. A barium enema with air contrast revealed foreshortening of the left colon with few haustral markings consistent with the previous surgery but with no constrictions, masses, or polyps. Gastrointestinal and small bowel series were normal except for delayed emptying of the small intestine with segmentation of barium.

A second strength tuberculin test was negative after 48 hours. Venous pressure in the arms and legs was normal. Circulation time was 14 seconds. The electrocardiogram was normal except for a diphasic T wave in lead II. Stools for ova, parasites, and enteric pathogens were negative.

Course: The patient was afebrile throughout her illness.

The hemoglobin was raised to 12 g/100 ml with 1,000 ml of blood, but fell again to 8.3 g/100 ml within eight weeks.

Her diarrhea was not suppressed by kaolin or paregoric. Repeat sigmoidoscopy revealed slightly edematous and friable mucosa with scattered hemorrhagic spots but no ulcers. Rectal biopsy showed only "chronic inflammation."

The urinary tract infection was treated with nitrofurantoin and chloramphenicol.

Nausea and vomiting continued and were not helped by the usual methods of therapy.

On March 7, 1960, blood urea nitrogen was found to be 147 mg/100 ml; potassium, 5.18, carbon dioxide, 18, chloride, 102, and sodium, 137 mEq/liter. The following day venous pH was 7.32; carbon dioxide, 14 mEq/liter; and venous carbon dioxide pressure, 28.5 mm Hg. The patient was treated with bicarbonate supplementation, aluminum hydroxide gel, calcium gluconate, and intravenous fluids without any significant fall in blood urea nitrogen and with aggravation of the edema. She became oliguric. Urine sediment on March 10, 1960, contained many pus cells and occasional granular casts. No hyaline or red cell casts were seen. Retrograde pyelography revealed normal calyces, pelvis, and ureter on the right. The left ureter could not be catheterized.

After the initial overhydration was stopped, her weight fell from 121 pounds on March 11, 1960, to 117 pounds on March 13.

The next day the blood pressure fell to 85/40 mm Hg. Sodium was 121, chloride, 83.9, carbon dioxide, 21.3 mEq/liter; venous carbon dioxide pressure, 33.8 mm Hg; and pH, 7.40. On March 9, urine chloride had been 22.1 mEq/24 hours. An eosinophile count was 50/mm^3. Urine collections for 17-ketosteroid excretion were invalid due to severe oliguria. A blood culture on March 14 was sterile.

The same day fingerprint edema and cloudy sensorium were noted. Sodium was 114, chloride, 79, potassium, 6.4, and carbon dioxide, 18.7 mEq/liter. A blood volume determination showed a 520 ml deficit in the red cell mass. Three hundred milliliters of 5% saline followed by 500 ml of packed red cells were given with no effect on the blood pressure. On March 15 hydrocortisone and metaraminol were administered; the blood pressure rose to 100/60 mm Hg. Eventually levarterenol was required to maintain the blood pressure.

On March 15 the patient had guaiac positive emesis. The hemoglobin was 14 g/100 ml. Nasogastric suction was begun and the contents of the stomach came back free of blood. One unit of whole blood was transfused and the blood pressure remained stable. On the following day, the blood pressure suddenly became unobtainable and the patient died.

Ante-mortem diagnoses were amyloidosis, Addison's disease, or both, with malabsorption syndrome.

Post-mortem Examination: Microscopically there were extensive amyloid deposits in small blood vessels and in the parenchyma of the spleen and right kidney. There were less extensive amyloid deposits in the liver, heart, adrenals, pancreas, and entire gastrointestinal tract.

The final pathologic diagnoses were the following:

1. Adenocarcinoma of the left kidney with metastases to the right kidney.
2. Generalized amyloidosis involving the spleen, right kidney, liver, heart, adrenals, pancreas, and the gastrointestinal tract, with clinical sprue.
3. Thrombosis of the right renal vein, inferior vena cava with nephrotic syndrome and uremia.
4. Multiple small pulmonary emboli secondary to the thrombosis.
5. Previous surgical resection of adenocarcinoma of the colon (11 years), no residual tumor found at post-mortem.
6. Pulmonary atelectasis, partial, bilateral, and a right pleural effusion.
7. Marantic endocarditis of the mitral valve.
8. Adenomatous polyp of the cecum.
9. Nodular thyroid.
10. Surgically absent uterus.

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Summario in Interlingua

Esseva revistate le protocollos necroptic del Centro Memorial pro Cancere e Morbos Affin a New York pro le dece-un annos ab 1948 ad 1958. Amyloidosis esseva trovate in 16 ex 4033 casos. Le incidentia (0,4%) esseva assi simile a illo trovate in un serie de necropsias de un hospital general.

Morbo de Hodgkin e myeloma multiple esseva representate con significativemente plus alte procentages in le gruppo de casos con amyloidosis que in le serie total del necropsias. Septe del 16 casos de amyloidosis (44%) esseva casos de morbo de Hodgkin; duo (12,5%) esseva casos de myeloma multiple. In le serie total de 4033 necropsias, 207 (5,13%) esseva casos de morbo de Hodgkin; 34 (0,84%) esseva casos de myeloma multiple. Le remanente septe casos de amyloidosis consisteva de un occurrentia cata un in lymphosarcoma e in canceres del recto, del pulmones, del cervice, del esophago, del renes, e del glandula sub-maxillar.

Le distribution secundo le organo interessate differeva in amyloidosis con cancere ab illo in amyloidosis primari (serie de Rukavina) e resimilava illo in amyloidosis secundari (serie de Dahlin) in tanto que un significativemente plus alte incidentia de affectiones del ren e un significativemente plus basse incidentia de affectiones cardiac e pulmonar esseva constatate. Del altere latere, le casos de amyloidosis con cancere resimilava amyloidosis primari e differeva ab amyloidosis secundari in tanto que illos monstrava un significativemente plus basse incidentia de affectiones de nodos lymphatic e del systema gastrointestinal. In plus, le gruppo del casos con amyloidosis e cancere differeva ab amyloidosis secundari per un significativemente plus basse incidentia de affectiones hepatic, adrenal, e pancreatic.

Ab le puncto de vista clinic, omne le gruppos esseva characterisate per anormalitates renal (elevate concentrationes de nitrogeno de urea del sanguine, hypoproteinemia, edema) e indefinite anormalitates del function hepatic. Le gruppo a cancere e amyloidosis habeva etiam un alte incidentia de febre, anemia, diarrhea, e splenomegalia (iste ultime a causa de un alte procentage de casos de lymphoma).

Le diagnose de amyloidosis associate con malignitate es rendite plus facile per le sequente factores: Proteinuria; hypoproteinemia; edema; syndrome nephrotic; elevate concentrationes de nitrogeno de urea del sanguine (specialmente in le absentia de hypertension); elevation del nivello de globulina alpha del sero con normalitate de globulina gamma e declino de albumina; splenomegalia; hepatomegalia con nonspecific anormalitates functional; diarrhea de forma intractabile; syndrome de malabsorption; positivitate del test a rubio Congo; plus que 10% de disparitate inter simultanee determinationes del volumine de sanguine per medio de radio-iodate albumina seral e per medio de blau de Evans; e positive biopsias renal, gingival, muscular, lingual, o cutanee in tincturation secundo van Gieson.

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The Use of Radioiron in the Study of Anemia

R. A. Bohannon, M.D., J. L. Hutchison, M.D., F.R.C.P. (C), and S. R. Townsend, M.D., F.A.C.P.

Montreal, Canada

The increasing use of radioisotopes in clinical medicine offers better means of understanding and quantitating physiological processes. Tracer techniques using isotopes of iron allow investigation of iron metabolism and erythropoietic function. Radioiron binds to transferrin, an alpha-1 globulin, which has the capacity of accepting two atoms of iron per molecule of protein. During its transport in the plasma, iron is removed from the plasma at an exponential rate into the bone marrow where it is soon utilized in hemoglobin synthesis. Normally only a small portion of iron leaves the plasma for storage. Subsequently, the tracer reappears in the peripheral circulation incorporated into new red cells. Senescent red cells are removed from the circulation by the reticuloendothelial system and degraded. Iron liberated from these cells is returned to the plasma where it is either redistributed into the body iron stores or transported to the bone marrow for re-utilization in erythropoiesis.

Radioiron studies provide data which can be of great usefulness clinically, especially with regard to understanding mechanisms of anemia. The availability of radioiron (Fe^{59}), the relative simplicity of apparatus required for isotope counting, and, in particular, new techniques for conducting radioiron studies have all contributed to making radioiron data more accessible for the clinician. Less time is required to process specimens of blood, making it feasible to apply these studies to the clinical situation.

The purpose of this paper is to present radioiron data obtained in studying patients with iron deficiency anemia and other types of anemia in which there is involvement of iron metabolism or a disturbance in erythropoiesis.

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Requests for reprints should be addressed to Richard A. Bohannon, M.D., Lymphoma Section, Sloan Kettering Institute, Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, New York.

Methods and Materials

Hemosiderin tests on bone marrow aspiration smears were performed after a modified method of Kaplan, Zuelzer, and Mouriquand (1). Slides were stained for 20 minutes with equal parts of freshly mixed 2% potassium ferrocyanide and 2% hydrochloric acid, but they were not fixed with formalin or counterstained with basic fuchsin.

Plasma iron and unsaturated iron binding capacity (UIBC) were measured by the method C of Laurell (2), modified by Davies, Levin, and Oberholzer (3).

Measurement of clearance of radioiron from the plasma and incorporation of radioiron into the circulating red cell mass was obtained by the technique of Lentino, Collica, and Rubenfeld (4).

The removal of radioiron from the plasma, where it is bound to transferrin as an iron-protein complex, to the tissues is measured by the time required for disappearance of one-half of the radioactivity of the radioiron initially given. This is designated as the $T_{\frac{1}{2}}$ clearance time and is expressed in minutes.

Plasma iron turnover is the net flux of iron removed from the plasma to tissues and re-entry of iron from tissue stores into plasma. Plasma iron turnover is measured in terms of mg iron per 100 ml of whole blood per day. The values for the plasma iron turnover were calculated from a formula used by Bothwell, Hurtado, Donohue, and Finch (5), which was modified

TABLE 1. Control Series

No.	Case	Age	Sex	Associated Condition	Hemoglobin g/100 ml	MCHC* %	Retics† %	Fe µg/100 ml Plasma	UIBC‡ µg/100 ml Plasma	$T_{\frac{1}{2}}$§ Mins.	Iron Turnover mg Fe/Day/100 ml Whole Blood
1.	E.G.	27	F	Barbiturate addiction	11.2	30	2.0	88	149	66	0.84
2.	M.K.	82	F	Dermatitis, nonspecific	11.4	30	2.0	138	162	114	0.73
3.	D.M.	50	F	Pustular bacterid of hands	13.8	31	0.5	88	233	116	0.43
4.	A.S.	66	F	Craniopharyngioma	14.6	30	1.8	53	261	68	0.39
5.	J.B.	65	M	Psoriasis	14.4	30	0.5	160	204	78	1.02
6.	J.C.	60	M	Myocardial infarction	16.1	30	3.0	167	176	96	0.74
7.	C.M.	49	M	Osteomyelitis, rt. tibia	14.8	31	0.5	100	212	64	0.82
8.	A.M.	49	M	Psoriasis	14.2	30	0.5	110	230	92	0.61
9.	E.Q.	33	M	Multiple sclerosis	14.6	31	1.0	110	108	76	0.78
10.	L.R.	41	M	Crush injury, left hand	14.4	30	0.5	70	230	72	0.52

* Mean corpuscular hemoglobin concentration.

† Reticulocytes.

‡ Unsaturated iron binding capacity.

§ Half-time.

TABLE 2. Iron Deficiency Anemia—Untreated

No.	Case	Age	Sex	Associated Condition	Hemoglobin g/100 ml	MCHC* %	Retics† %	Bone Marrow Hemosiderin	Fe μg/100 ml Plasma	UIBC‡ μg/100 ml Plasma	$T_{\frac{1}{2}}$§ Min.	Iron Turnover mg Fe/Day/100 ml Whole Blood
11.	W.B.	74	M	Chronic duodenal and stomal ulcers, bleeding	9.8	26	3.0	Absent	40	159	31	0.93
12.	A.B.	75	M	Arteriosclerotic heart disease, congestive heart failure	8.8	23	1.6	Absent	18	200	17	0.66
13.	J.C.	72	M	Carcinoma of stomach	3.9	22	2.8	Absent	15	252	18	0.68
14.	E.C.	64	F	Hypothyroidism	7.8	26	3.6	Absent	33	356	22	1.06
15.	R.E.	85	M	Nodular hyperplasia prostate	11.1	28	1.0	Absent	33	228	40	0.50
16.	J.F.	60	F	Hiatus hernia	6.8	28	2.2	Absent	18	218	18	0.78
17.	F.K.	39	M	Ulcerative colitis	5.4	23	2.4	Absent	27	227	16	1.30
18.	F.L.	40	F	Laennec's cirrhosis and varices	8.7	29	2.6	Absent	37	308	24	1.08
19.	A.M.	54	F	Gastroenterostomy	8.9	26	3.0	Absent	33	307	36	0.61
20.	G.L.	39	M	Rheumatoid spondylitis; gastric ulcer; nephrocalcinosis	7.6	24	1.8	Absent	27	164	24	0.78
21.	C.P.	82	M	Fracture, right humerus	10.4	29	1.6	Absent	37	184	50	0.48
22.	A.S.	52	M	Adenomatous polyp, recto-sigmoid	9.3	27	1.0	Absent	27	273	22	0.80
23.	A.W.	85	F	Diverticulosis	10.6	30	0.5	Absent	54	197	36	0.98
24.	A.B.	80	F	Arteriosclerotic heart disease, congestive heart failure Carcinoma of asc. colon	8.9	25	0.5	—	23	295	14	1.05
25.	E.B.	66	F	Carcinoma of stomach	11.1	29	1.2	—	33	136	21	0.97
26.	J.F.	89	F	Squamous cell carcinoma of face	7.9	27	2.0	—	27	234	28	0.70
27.	S.K.	60	F	Hiatus hernia	11.2	29	1.4	—	40	256	34	0.73
28.	A.L.	68	M	Internal hemorrhoids	8.8	26	2.0	—	18	306	15	0.79
29.	J.R.	46	F	Fibromyomata uteri	7.6	25	1.4	—	27	240	20	0.94
30.	C.W.	86	F	Carcinoma of asc. colon	10.0	27	2.6	—	23	249	31	0.48
31.	D.W.	59	F	Carcinoma of cecum	6.5	26	2.0	—	33	291	21	1.18

* Mean corpuscular hemoglobin concentration.
† Reticulocytes.
‡ Unsaturated iron binding capacity.
§ Half-time.

TABLE 3. Iron Deficiency Anemia—Receiving Therapy at Time Ferrokinetic Studies Performed

No.	Case	Age	Sex	Associated Condition	Hemoglobin g/100 ml	MCHC* %	Retics† %	Bone Marrow Hemosiderin	Fe μg/100 ml Plasma	UIBC‡ μg/100 ml Plasma	$T_{\frac{1}{2}}$§ Min.	Iron Turnover mg Fe/Day/100 ml Whole Blood	Treatment
32.	E.B.	47	F	Peptic ulcers, pyloroduodenal and gastric	11.4	30	2.8	Absent	90	185	29	1.96	Blood
33.	L.C.	68	F	Carcinoma of cervix	4.8	21	4.6	—	88	304	14	4.84	Blood
34.	D.D.	37	F	Leiomyoma uteri	7.5	27	5.0	—	126	275	33	2.78	Oral iron
35.	J.D.	67	M	Adenocarcinoma of asc. colon	10.7	26	1.0	Absent	90	329	42	1.26	Oral iron
36.	R.D.	39	M	Internal hemorrhoids	7.5	23	2.6	Absent	62	238	17	2.56	Oral iron
37.	J.H.	86	M	Carcinoma of stomach	9.1	28	1.6	Absent	40	178	18	1.51	Blood
38.	C.J.	82	M	Arteriosclerotic heart disease and congestive heart failure	3.7	19	2.8	Absent	57	259	16	2.88	Oral iron and blood
39.	W.M.	72	M	Adenomatous polyp of rectum	7.9	26	10.0	Absent	45	252	25	1.30	Oral iron

* Mean corpuscular hemoglobin concentration.
† Reticulocytes.
‡ Unsaturated iron binding capacity.
§ Half-time.

TABLE 4. Hemolytic Anemia

No.	Case	Age	Sex	Condition	Hemoglobin % g/100 ml	MCHC* %	Retics† %	Fe μg/100 ml Plasma	UIBC‡	T½§ Min.	Iron Turnover mg Fe/Day/100 ml Whole Blood
40.	O.B.	60	M	Ac. hemolytic anemia; metastatic cancer stomach	4.8	30	30.6	110	108	59	1.59
41.	J.B.	56	M	Myelofibrosis	9.8	29	9.0	72	—	36	1.34
42.	E.D.	81	F	Ac. hemolytic anemia	12.3	31	4.0	72	184	15	3.02
43.	R.F.	47	M	Lymphosarcoma	7.1	30	2.6	50	159	36	1.06
44.	A.H.	68	F	Ac. hemolytic anemia	7.6	33	3.0	103	96	48	1.65
45.	M.J.	51	F	Chronic myelogenous leukemia	7.6	30	2.0	58	193	17	2.56

* Mean corpuscular hemoglobin concentration.
† Reticulocytes.
‡ Unsaturated iron binding capacity.
§ Half-time.

from the formula derived by Huff, Hennessy, Austin, Garcia, Roberts, and Lawrence (6).

Incorporation of radioiron into the circulating red cell mass was usually measured on the eighth day after administration of radioiron, at which time values for incorporation have ordinarily reached a plateau, in the same manner as described by Lentino et al. (4). Incorporation is measured in per cent and indicates the amount of tracer iron used in hemoglobin synthesis relative to that administered.

All patients studied were ward patients at The Montreal General Hospital. Fifty-one patients studied comprised five main groups:

A. Control series (ten patients).
B. Untreated iron deficiency anemia (21 patients).
C. Iron deficiency anemia with therapy (eight patients).
D. Hemolytic anemia (six patients).
E. Anemia due to erythroid hypoplasia (six patients).

Other patients having pernicious anemia, anemia of infection, and unclassified types of anemia have been studied but are not included in the results because they represent heterogeneous groups too small for statistical analysis and comparison.

Results

The indications for hospital admission and pertinent hematological and radioiron data in each case are listed in Tables 1 through 6.

A. CONTROL SERIES

The range of half-time of clearance of radioiron from the plasma in normal patients varied from 66 to 116 minutes (Table 1). Individual values for half-time of clearance are plotted in Figure 1. The determined values for half-time of clearance of this group of ten patients correspond closely to the range of 60 to 120 minutes given for normal subjects by Loeffler (7). The mean value for half-time of clearance of radioiron from the plasma was 84.2 minutes, and the standard deviation (SD) was 11.6 minutes.

The normal range of iron turnover varied from 0.39 to 1.02 milligrams iron per 100 milliliters whole blood per day (Figure 2). The mean value of 0.69 milligram iron per 100 milliliters whole blood per day corresponds to the values given by Bothwell et al. (5) of 0.61 milligram iron in normal subjects and 0.50 milligram in hematologically normal hospitalized patients.

Incorporation of radioiron in the circulating erythrocyte mass was in excess of 80% by the eighth day after administration of radioiron in all ten patients of the control series.

TABLE 5. Statistical Analysis of Radioiron Data

	$T_{\frac{1}{2}}$* Plasma Clearance of Radioiron Minutes			Iron Turnover mg Fe/Day/100 ml Whole Blood		
	Range	Mean Value	SD†	Range	Mean Value	SD†
Normal controls (10 cases)	66–116	84.2	11.6	0.39–1.02	0.69	0.18
Iron deficiency—untreated (21 cases)	14–50	25.6	9.3	0.48–1.30	0.83	0.16
Iron deficiency—treated (8 cases)	14–42	24.0	9.1	1.26–4.84	—	—
Hemolytic anemia (6 cases)	15–59	35.6	14.6	1.06–3.02	—	—
Anemia due to erythroid hypoplasia (6 cases)	124–470	267	—	0.28–0.84	0.51	0.20

* Half-time.
† Standard deviation.

TABLE 6. Delayed Clearance of Radioiron from the Plasma

No.	Case	Age	Sex	Condition	Hemoglobin g/100 ml	MCHC* %	Retics† %	Fe μg/100 ml Plasma	UIBC‡	$T_{\frac{1}{2}}$§ Min.	Iron Turnover mg Fe/Day/100 ml Whole Blood	Fe-59 RBC‖ Incorporation %
46.	A.T.	25	M	Idiopathic aplastic anemia	13.4	34	2.6	315	zero	355	0.54	24
47.	A.M.	74	M	Myelofibrosis	8.8	33	1.0	—	—	154	—	41
48.	S.P.	82	M	Chronic lymphocytic leukemia	7.6	29	1.0	177	—	470	0.28	2
49.	V.M.	86	F	Refractory anemia, cancer of breast, hepatitis	6.7	28	0.5	330	zero	300	0.84	10
50.	E.B.	52	F	Metastatic cancer of breast	8.3	29	2.0	126	zero	200	0.45	39
51.	B.D.	69	F	Osteochondrosarcoma, left knee; bone marrow depression secondary to nitrogen mustard therapy	15.9	30	0.5	115	165	124	0.45	25

* Mean corpuscular hemoglobin concentration.

† Reticulocytes.

‡ Unsaturated iron binding capacity.

§ Half-time.

‖ Red blood cell.

B. UNTREATED IRON DEFICIENCY ANEMIA

All patients with untreated iron deficiency anemia showed a rapid clearance of iron from the plasma (Table 2). Values ranged from 14 to 50 minutes in contrast to the normal values of 66 to 116 minutes (Figure 1). Iron turnover values ranged from 0.48 to 1.30 milligrams iron per 100 milliliters whole blood per day (Figure 2). The mean value was 0.83 milligram (normal, 0.69 milligram). Incorporation of radioiron in the circulating red cell mass was rapid and complete. Complete or 100% incorporation was not infrequently noted by the fourth day following administration of radioiron.

C. IRON DEFICIENCY ANEMIA WITH THERAPY

Patients with iron deficiency anemia who were treated with blood, oral iron, or both at some time within a 24-hour period before commencement of radioiron studies also demonstrated rapid clearance of radioiron from the plasma (Figure 1), and rapid and complete incorporation of radioiron in the circulating red cell mass (Table 3). The range of values for half-time clearance was 14 to 42 minutes. The mean value was 24 minutes, and standard deviation was 9.1 minutes. Iron turnover values for patients with iron deficiency anemia receiving treatment were greater than for patients in the untreated group. The range of values in the treated group varied from 1.26 to 4.84 milligrams iron per 100 milliliters whole blood per day (Figure 2).

D. HEMOLYTIC ANEMIA

Six patients were studied who had anemia due completely or in part to a hemolytic process (Table 4). The half-time of clearance values ranged from 15 to 59 minutes, and the mean value was 35.6 minutes with a standard deviation of 14.6 minutes (Figure 1). Iron turnover values were increased above the control group. They varied widely in these six patients from 1.06 to 3.02 milligrams iron per 100 milliliters whole blood per day (Figure 2).

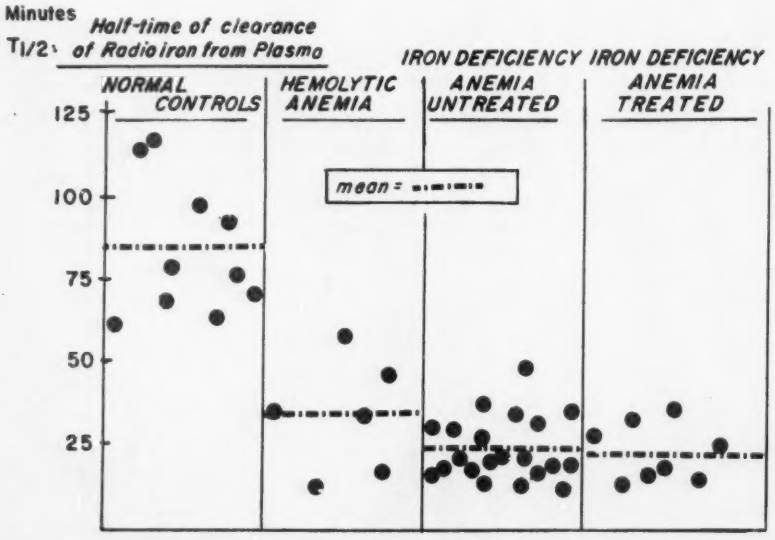

FIGURE 1. Values for half-time of clearance of radioiron from the plasma as determined in normal patients and in patients with hemolytic anemia and with iron deficiency anemia.

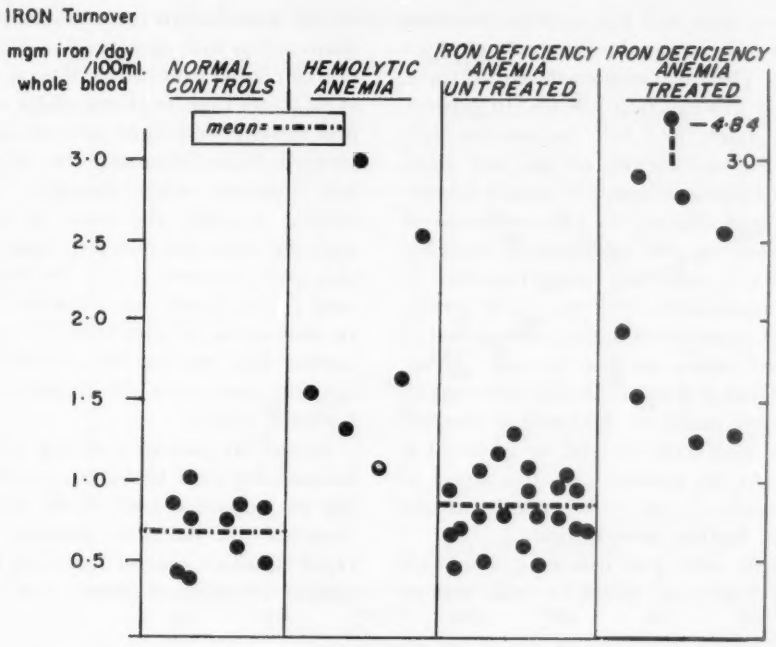

FIGURE 2. Values for iron turnover in normal patients and in patients with hemolytic anemia and with iron deficiency anemia.

E. ANEMIA DUE TO ERYTHROID HYPOPLASIA

A miscellaneous group of six patients had anemia because of depression of erythropoiesis. In two instances, the cause of erythroid hypoplasia was idiopathic, acquired, aplastic anemia. Marrow replacement by myelofibrosis, leukemia, and metastatic carcinoma, respectively, accounted for anemia in three cases, and marrow depression consequent to large doses of nitrogen mustard therapy was felt to be the cause of anemia in the last case. Clearance time of radioiron from the plasma was prolonged in all these cases and values ranged from 124 to 470 minutes. The mean value was 267 minutes. Iron turnover values varied from 0.28 to 0.84 milligram iron with a mean of 0.51 milligram iron and standard deviation of 0.20 milligram iron. Incorporation of radioiron in erythropoiesis, measured on the eighth day of radioiron study, was low in all cases. A range of 2 to 41% incorporation was obtained. The radioiron data for these five groups are summarized in Table 5.

DISCUSSION

From the results obtained in these studies of radioactive iron in association with anemia it becomes obvious that they naturally divide themselves into two groups: (a) conditions in which clearance of radioiron from the plasma is rapid; and (b) conditions in which the clearance is delayed.

CONDITIONS IN WHICH CLEARANCE IS RAPID

In iron deficiency anemia, it would appear that the more severe the anemia, as measured by the level of hemoglobin of peripheral blood, the faster will radioactive iron be removed from the plasma. This relationship is presented in Figure 3. A curve representing the relationship between

clearance time and hemoglobin level was constructed using the method of least squares. The calculated coefficient of correlation of this function was 0.8. In general, as the plasma iron falls in patients with iron deficiency anemia, so also will clearance of radioiron from the plasma become more rapid (Figure 4). The coefficient of correlation for this relationship, however, is only 0.6, indicating that exceptions to this generalization will not infrequently occur. A paradoxical finding was normal or increased values for iron turnover in untreated iron deficiency. Similar observations have been made by Bothwell, Callender, Mallett, and Witts (8), and by Bothwell et al. (5). At the present time, this aspect of iron kinetics is not fully understood and requires further investigation.

Patients with iron deficiency who were treated with iron, blood, or both demonstrated a marked increase in iron turnover. Inasmuch as iron turnover is a direct function of plasma iron and an inverse function of clearance time, explanation for increased iron turnover in treated patients is straightforward. With treatment, the plasma iron was increased while clearance time remained virtually the same as compared with the untreated group. It follows, then, that iron turnover would be elevated so long as the plasma iron remained elevated. In none of the patients with iron deficiency anemia who received iron, blood, or both did treatment alter the clearance of iron from the plasma.

Studies on patients suffering from a significant degree of blood loss but who have not yet exhausted body stores of iron and therefore are not iron deficient show a rapid clearance time of radioiron from the plasma, elevation of plasma iron turnover,

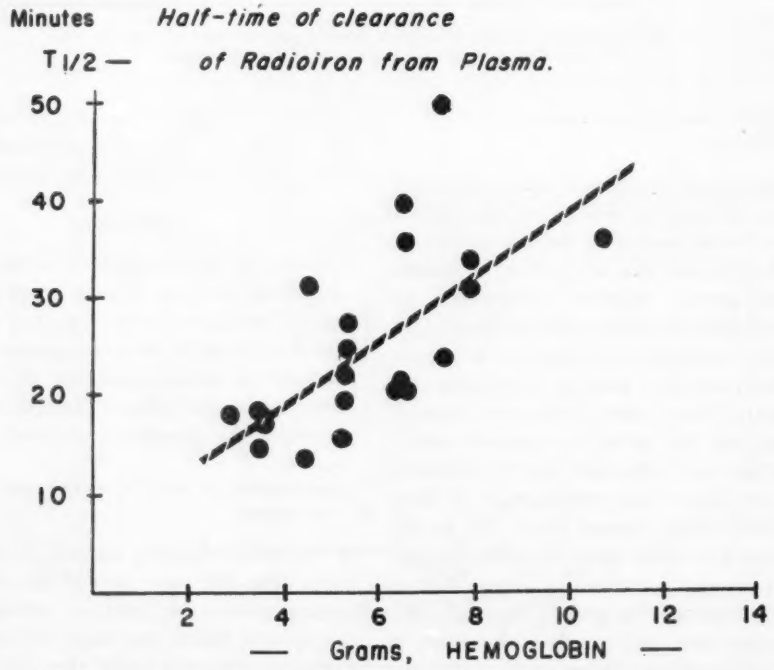

FIGURE 3. The relationship between the half-time of clearance of radioiron from the plasma, in minutes, and the degree of anemia, in grams of hemoglobin per 100 milliliters blood, in patients with untreated iron deficiency anemia.

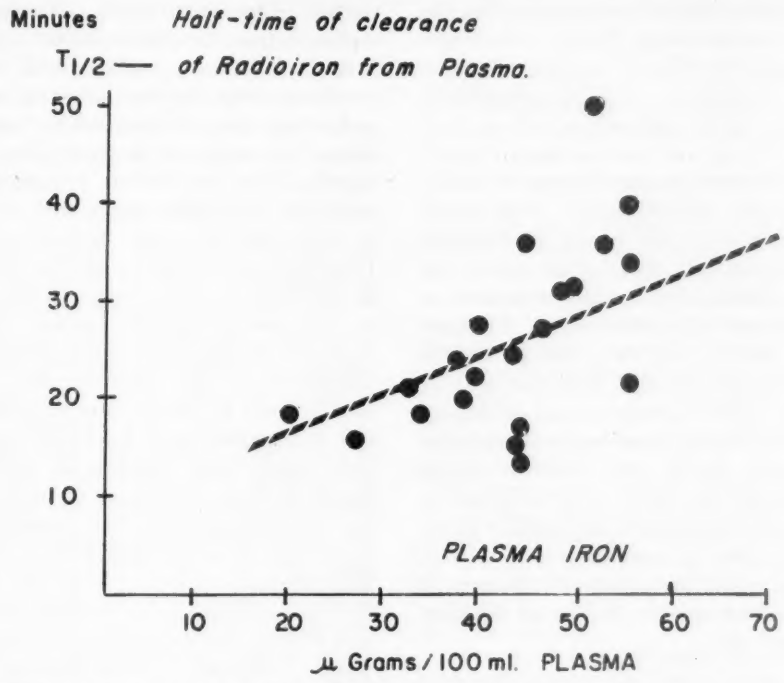

FIGURE 4. The relationship between the half-time of clearance of radioiron from the plasma, in minutes, and the level of the plasma iron, in micrograms per 100 milliliters plasma, in patients with untreated iron deficiency anemia.

and normal incorporation of radioiron into the circulating red cell mass, data similar in all respects to those obtained from patients with iron deficiency under therapy.

E. C., a 64-year-old white female (Case 14) with iron deficiency anemia complicated by hypothyroidism, is of some interest. In hypothyroidism a normocytic anemia may arise on the basis of decreased activity of erythropoietic marrow function. Such an anemia is often reversed when treated with desiccated thyroid gland (9). Radioiron in this patient was removed rapidly from plasma and utilized completely. Had erythropoietic marrow function been depressed by the hypothyroid state, such data would not have been obtained. A second case of hypochromic anemia in association with hypothyroidism has proven to be similar and has responded in the same manner to radioiron as have all other patients with untreated iron deficiency anemia.

In hemolytic anemia and hemolytic disorders inference as to the degree of bone marrow compensation can be obtained by determining the value for the iron turnover. The greater the iron turnover, the greater is the degree of marrow activity and marrow compensation. E. D. (Case 42), a female with idiopathic acquired, Coombs'-positive, hemolytic anemia, maintained a satisfactory level of hemoglobin on steroid therapy. This controlled the hemolytic process to an extent sufficient that bone marrow compensation could restore the hemoglobin level of peripheral blood to normal or near normal levels. The marked elevation of the iron turnover suggested that the hemolytic process was still active and that steroid withdrawal could not yet

be considered as late as nine years after the onset of the hemolytic process. A male patient (Case 41) with a myeloproliferative disorder developed a hemolytic process with shortening of the radioactive sodium chromate (Cr^{51}) red cell survival time. His illness had evolved through phases of thrombocythemia, polycythemia, leukocytosis with immaturity, and finally myelofibrosis with myeloid metaplasia of the spleen and anemia. Radioiron studies indicated an iron turnover of approximately 1.5 times normal. In this case, then, anemia was due to a combined effect of hemolysis and incomplete marrow compensation of hemolysis. The enlarged spleen was probably playing a hypersplenic role, and the partial replacement of normal marrow tissue by myelofibrosis explained the inability of the bone marrow to compensate completely. This case illustrates well the concept of relative bone marrow failure as discussed by Moore (10).

CONDITIONS IN WHICH CLEARANCE OF RADIOIRON FROM THE PLASMA IS DELAYED

The function of the erythroid marrow tissue can be depressed in a variety of clinical situations (Table 6). Erythroid marrow hypoplasia of undetermined etiology may be congenital or acquired and may be associated with anemia only—so-called refractory anemia—or it may be associated with pancytopenia in which case it is referred to as aplastic anemia. Refractory or aplastic anemia may be attendant upon use of chemotherapeutic agents having antimitotic activity, other types of chemical insult to the marrow, or irradiation injury to the marrow. Erythroid marrow hypoplasia also ensues when erythroid marrow tissue is replaced by proliferating tissue as in myelofibrosis, osteosclerosis, metastatic tumor, or leukemia.

In considering the severity of erythroid marrow hypofunction due to any cause, a direct approach is the use of radioiron studies. Characteristically, clearance of radioiron from the plasma is slow, the half-time of clearance often being well beyond two hours. Iron turnover is low or normal, and incorporation of iron into new red cells is low. In conditions of erythroid marrow hypofunction, two factors operate to decrease the usefulness of the iron turnover as reflecting erythroid marrow activity. First, iron metabolism is usually disturbed so that hyperferremia, often to the extent of saturation of the iron binding capacity, is present. In the second place, although the component of iron turnover which measures removal of plasma iron to bone marrow is decreased when erythroid hypofunction exists, that component measuring transport from iron stores to plasma may not be. Consequently, iron turnover can have a certain, measurable, basal level, even in the event of total marrow aplasia. Hence, the more reliable index of erythroid marrow activity when erythroid marrow hypoplasia is present is measurement of the extent of incorporation of radioiron into newly formed red cells.

Radioiron studies made a singular contribution to clarification of the mechanism of anemia in S. P. (Case 48), an 82-year-old widower with chronic, lymphocytic leukemia. During the 11 months following the initial diagnosis of leukemia, the patient developed severe anemia and required numerous blood transfusions. There was no evidence of a hemolytic mechanism. But on two occasions, there was evidence of considerable gastrointestinal blood loss. Radioiron studies revealed a plasma iron of 177 micrograms per 100 milliliters plasma, a half-time of clearance of 470 minutes, an iron turnover of 0.28 milligram iron per 100 milliliters whole blood per day, and only 2% incorporation of radioiron in the circulating red cell mass. At autopsy, the characteristic findings of chronic lymphocytic leukemia were seen. In particular, the marrow spaces were extensively replaced by the leukemic process. Blood loss

was certainly a factor in this patient's anemia. But the elevated plasma iron did not suggest an iron deficiency state. Radioiron studies, though, demonstrated dramatically that the principal mechanism for anemia was a severe degree of erythroid marrow hypoplasia.

Summary

1. Hematologic and radioiron data are presented for 51 patients investigated at The Montreal General Hospital.

2. Ten patients comprised a control series. The remainder had hemolytic anemia, iron deficiency anemia, or anemia due to marrow hypofunction.

3. Radioiron data were supplemented by the medical case history in selected instances so that the clinical usefulness of radioiron data could be demonstrated.

4. Current techniques for obtaining radioiron data permit reliable data to be obtained with facility from the routine hospital isotope laboratory and thus permit potentially greater applicability of radioiron data in clinical medicine.

Acknowledgments

We wish to express gratitude to R. Beique, Ph.D., and E. H. Bensley, M.D., for their counsel and cooperation in connection with these studies. We are indebted to D. G. Cameron, M.D., Physician-in-Chief of The Montreal General Hospital and Professor of Medicine at McGill University, and attending physicians at The Montreal General Hospital for permission to study patients in their care.

Summario in Interlingua

Studios a ferro radioactive esseva effectuate in 51 patientes al Hospital General Montreal, con le objectivo de obtener un meliorate comprension del mechanismos de anemia e de assecurar un plus precise determination quantitative del metabolismo de ferro e del erythropoiese. Le patientes studiate esseva gruppate in cinque major categorias. Iste categorias esseva (1) un serie de controlo de 10 subjectos, (2) un serie de casos de non-tractate anemia a carentia de ferro de 21 patientes, (3) un serie de casos de anemia a carentia de ferro sub tractamento de octo patientes, (4) un serie de sex casos de anemia hemolytic, e (5) un serie de sex casos de anemia causate per hypoplasia erythroide. Esseva effectuate un analyse statistic del clearance de ferro radioactive e de datos concernente le metabolismo de ferro. In omne iste respectos, le cinque gruppos esseva comparate.

Patientes con anemia a carentia de ferro demonstrava un rapide clearance del ferro radioactive ab le plasma. Esseva notate que quanto plus sever esseva le anemia (a judicar per le nivello de hemoglobina) tanto plus rapidemente esseva le ferro radioactive eliminate ab le plasma. Esseva confirmate le constatation paradoxe per altere investigatores que il occurre in non-tractate anemia a carentia de ferro que le metabolismo de ferro es augmentate. Patientes in carentia de ferro qui se trovava sub tractamento habeva frappante augmentos del metabolismo de ferro.

Le patientes con disordine hemolytic habeva un rapide clearance de ferro radioactive ab le plasma e augmentate valores del metabolismo de ferro. Inferentias con respecto al grado del compensation osseo-medullari esseva possibile per notar le grado del augmentos in le metabolismo de ferro.

Patientes con anemia causate per hypoplasia erythroide del medulla habeva retardate clearance de ferro radioactive ab le plasma. Illes habeva valores normal o basse pro le metabolismo de ferro e un incomplete incorporation de ferro radioactive in le erythropoiese. Es discutite le these que datos concernente le incorporation de ferro es plus fidel como indices del activitate erythroide in casos de hypoplasia erythroide que datos concernente le metabolismo de ferro.

Le datos obtenite per medio de ferro radioactive esseva supplementate per le historia clinic del patiente in certe seligite casos, de maniera que le utilitate clinic del datos de ferro radioactive poteva esser emphatisate. Es opinate que le technicas currentemente disponibile permitte al typic laboratorio isotopologic de hospital obtener fidel datos de ferro radioactive sin grande difficultates, de maniera que le application plus general de datos de ferro radioactive al studio de anemia es potentialmente possibile.

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CASE REPORTS

Cardiac Amyloidosis

Two Cases with Digitalis Sensitivity

JAMES T. CASSIDY, M.D., *Ann Arbor, Michigan*

GENERALIZED AMYLOIDOSIS is an uncommon disorder; the approximate frequency at autopsy is 0.5%. It is, however, a subject of frequent diagnostic consideration because of its diversified clinical manifestations. The heart is affected to a significant degree in 40 to 90% of cases (1–4). Such involvement was responsible for major disability in two patients, one with primary amyloidosis, the other with amyloidosis secondary to plasmacytoma. Observations in these cases which might suggest amyloid infiltration as a cause for obscure heart disease are discussed, with particular attention to a previously unreported sensitivity to digitalis.

CASE REPORTS

CASE 1

A 58-year-old farmer was admitted on June 24, 1959, with fatigue of ten months' duration. For seven months he had noted diarrhea, abdominal cramping and bloating, anorexia, weight loss, jaundice, and dark urine. Dyspnea and ankle edema subsequently developed.

Physical examination showed an icteric and emaciated white male who appeared to be chronically ill. Blood pressure was 120/70 mm Hg. Pulse was 80/minute and irregular. Ocular fundi and tongue were normal. Bilateral fine and coarse râles were heard throughout both lung fields on inspiration. The diaphragms were low and excursion was limited. Neck veins were not distended. The left border of cardiac dullness was halfway between midclavicular and anterior axillary lines. A minimal, left parasternal systolic lift and a forceful, localized systolic apical impulse were felt. The first apical sound was loud and snapping. The second pulmonic sound was palpable and accentuated and exhibited fixed splitting. A harsh ejection systolic murmur was loudest at the left sternal border in the third intercostal space. The liver was firm, smooth, and slightly tender but was not definitely enlarged. Moderate ankle edema was present.

Hemoglobin was 11.1 g/100 ml, hematocrit, 38%, and red cell count, 3.8 million/mm^3. White cell count was 6,700/mm^3 with a normal differential. Urinalysis revealed 1+ bilirubin. Serum bilirubin was 11.6 mg/100 ml with a one-minute direct fraction of 5.7 mg/100 ml. Alkaline phosphatase was 28.8 King-Armstrong units. Total serum protein was 5.5 g/100 ml; albumin, 41%; alpha-1, 6%; alpha-2, 19%; beta, 18%; and gamma, 16%. Serum glutamic oxaloacetic transaminase was 35 units. Prothrombin concentration remained approximately 25% despite repeated intravenous administration of vitamin K-1. Venous pressure was 80 mm of physiologic saline. Fluoroscopy demonstrated moderate, generalized cardiac enlargement with limited pulsation of all borders.

An electrocardiogram (Figure 1, top) showed atrial fibrillation with a ventricular rate of 75, QRS interval of 0.12 second, and QT interval of 0.45 second. Intraventricular block, probably of the left bundle branch type, was present. There were flat or slightly inverted T waves in the limb leads and in V_6. An R wave was absent in V_3 and V_4 suggesting old anteroseptal infarction.

Digitoxin 0.8 mg was given orally on July 8; the serum potassium was 4.8 mEq/liter. On July 9, digitoxin was omitted because the pulse was 60. On July 10, 0.1 mg was given. Extreme cardiac irregularity occurred until July 15, when another 0.1 mg was given; the serum potassium was 5 mEq/liter. The cardiac rate subsequently slowed to approximately 30 and no further digitoxin was administered.

An electrocardiogram (Figure 1, bottom) on July 15 was identical to the previous tracing except for a ventricular rate of 31 with frequent ventricular premature beats.

Extrahepatic biliary obstruction could not be eliminated. Exploratory celiotomy was therefore performed on July 17. The liver was firm and mottled green, and obstruction of the common bile duct was not found. A definite diagnosis could not

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From the Department of Internal Medicine, University Hospital, Ann Arbor, Michigan.

Requests for reprints should be addressed to James T. Cassidy, M.D., Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan.

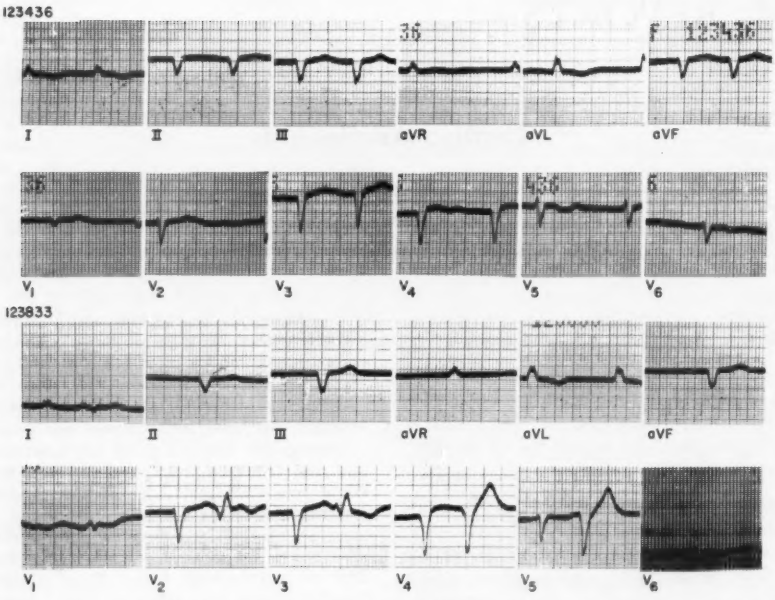

FIGURE 1. (*Case 1.*) Top electrocardiogram shows atrial fibrillation with ventricular rate of 75, QRS interval of 0.12 second, and QT interval of 0.45 second. Bottom electrocardiogram taken July 15 is identical to previous tracing except for ventricular rate and premature beats.

be made, and biopsy of the liver was done. The patient died three days later in shock.

Autopsy showed generalized amyloidosis with extensive infiltration of mesenchymal tissues including heart, smooth muscle of gastrointestinal and genitourinary tracts, and blood vessels. There was less involvement of liver, spleen, kidneys, adrenal glands, prostate, testes, pancreas, gall bladder, thyroid gland, larynx, bronchopulmonary tract, and adipose tissue. Methyl violet and Congo red stains were faintly positive. The heart weighed 430 g. The left ventricular wall measured 13 mm and the right 2 to 7 mm. There was minimal atherosclerosis of the coronary arteries. There were extensive deposits of amyloid in the myocardium, especially surrounding atrophic myofibrils, in endocardium and subepicardium adipose tissue, and in the walls of arteries and veins. There was minimal thickening of mitral and tricuspid valves with amyloid. The liver weighed 1,300 g. Obstructive icterus was present along with extensive amyloid infiltration between endothelial cells of sinusoids and hepatic cords, and in blood vessels of portal triads.

CASE 2

A 66-year-old seamstress was admitted on November 17, 1958, for a tumor of the right chest which had been enlarging for two years, and for numbness, pain, and awkwardness of the first three fingers of each hand of six months' duration.

Physical examination showed an obese white female. Blood pressure was 185/100 mm Hg. There was atrophy of thenar muscles, and hypesthesia was noted in the distribution of the median nerve of each hand. A hard, nontender right anterior chest wall mass of 10 by 10 by 4 cm was present.

Routine laboratory studies were normal. Total serum protein was 8.2 g/100 ml; albumin, 34%; alpha-1, 4%; alpha-2, 10%; beta, 9%; gamma, 11%; and a slower, sharply-peaked abnormal band 32%. X-ray films revealed extensive destruction of right second rib. Biopsy of the mass was interpreted as a plasmacytoma. Sternal marrow aspiration was not diagnostic of multiple myeloma.

Irradiation therapy was directed to the tumor; operative release of the left volar transverse carpal ligaments was performed. Postoperatively, the patient experienced immediate relief in the left hand and improvement in the right over the next year. She was re-admitted on October 13, 1959, with progressive dyspnea of nine months' duration. During the four months prior to admission she had noted increasing abdominal girth and more recently had noted ankle edema and paroxysmal nocturnal dyspnea.

The patient appeared to be chronically ill. Blood pressure was 110/75 mm Hg. Marked peripheral edema was present. Ocular fundi and tongue were normal. Neurologic changes in the hands were present but less marked. The chest wall mass had

decreased in size to 8 by 6 by 5 cm. The right thorax was dull to percussion, and basilar, moist râles were heard bilaterally. Moderate neck vein distention was noted. There was marked cardiomegaly. A paradoxical pulse was present. An apical protodiastolic extra sound and accentuation and paradoxical splitting of the basal second sound were noted. A soft, regurgitant apical systolic murmur was heard. The liver extended 9 cm below the right costal margin. Ascites was present.

Hemoglobin was 10.9 g/100 ml, hematocrit, 36.5%, and red cell count, 3.8 million/mm³. White cell count was 7,450/mm³ with a normal differential. Rouleaux of red cells were prominent. Urinalysis revealed Bence Jones proteinuria. Blood urea nitrogen was 32 mg/100 ml. Serum protein electrophoresis was similar to the previous determination. Venous pressure was 260 mm of physiologic saline, and sodium dehydrocholate circulation time was 40 seconds. Sternal marrow aspiration was repeated and was not diagnostic.

An electrocardiogram (Figure 2, top) showed a rate of 80, PR interval of 0.20 second, QRS interval of 0.08 second, and QT interval of 0.36 second. Right axis deviation was present. There were occasional ventricular premature beats. Partially inverted T waves were seen in all standard leads and in V_3 through V_6.

Digitalis was started on October 13. Varying arrhythmias with rates as slow as 50 developed after a total of 1.3 g of digitalis folia over the next 60 hours. The drug was therefore discontinued; the serum potassium was 3.9 mEq/liter.

An electrocardiogram (Figure 2, bottom) on October 15 showed a rate of 70, QRS interval of 0.08 second, and QT interval of 0.36 second. Bigeminy was almost continuously present, and both complexes of each pair were similar. P waves were present only before the second complexes. A-V nodal rhythm of the second type was suggested with retrograde stimulation.

The patient was somnolent and unresponsive to diuretics. An irregular tachycardia persisted. There was gradual elevation of the serum potassium level which reached 8.3 mEq/liter on October 31, when the patient complained of severe subxiphoid pain. The electrocardiogram showed atrial fibrillation with a ventricular rate of 73 and changes incident to hyperkalemia. The following day the patient died with vasomotor collapse.

Autopsy showed generalized amyloidosis with extensive infiltration of mesenchymal tissues including

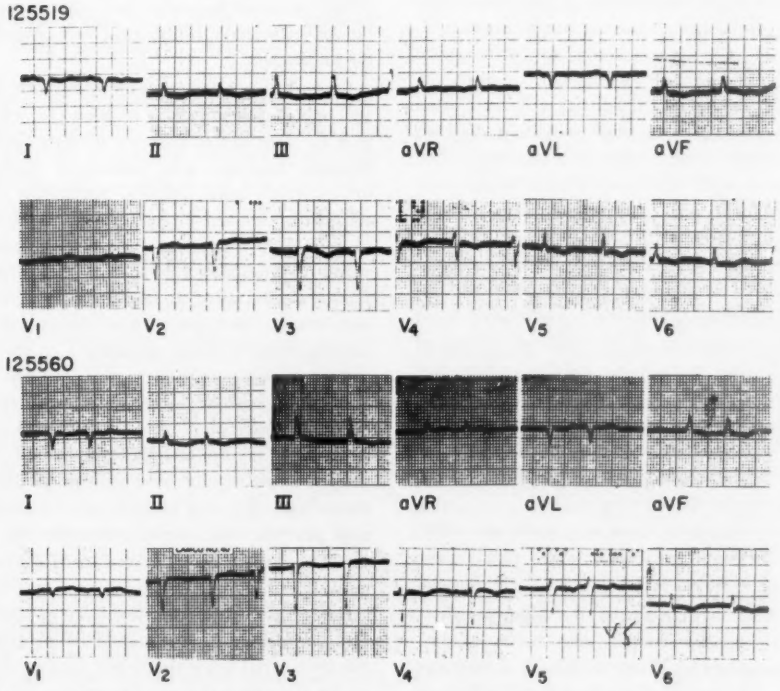

FIGURE 2. (*Case 2.*) Top electrocardiogram shows rate of 80, PR interval of 0.20 second, QRS interval of 0.08 second, and QT interval of 0.36 second. Bottom shows tracing of October 15, with bigeminy almost continuously present.

heart, smooth muscle of gastrointestinal and genitourinary tracts, and blood vessels. There was less involvement of thyroid gland, gall bladder, and lungs. The amyloid was not metachromatic with methyl violet, but had moderate affinity for Congo red. Minimal ascites, moderate right pleural effusion, and 225 ml of clear pericardial fluid were found. An encapsulated, solitary plasmacytoma consisted of mature plasma cells and had extensive deposition of amyloid with many foreign body giant cells. The heart weighed 680 g, was dilated, and grossly appeared to be infiltrated. The left ventricular wall measured 18 mm and the right 3 mm. Valve leaflets were thin and delicate. There was minimal coronary atherosclerosis. Diffuse and extensive amyloid deposition was present in the myocardium with atrophy of myofibrils. There was less extensive infiltration of the walls of small vessels and of subepicardial adipose tissue.

Discussion

In the first patient the combination of liver disease and heart failure suggested the diagnosis of amyloidosis. It is uncommon for signs of liver involvement to dominate the clinical picture and this case has been reported (5) as an example of the association of this disease and jaundice (6). Although the cardiac findings indicated pulmonary hypertension, the presence of atrial fibrillation was somewhat against cor pulmonale as the sole lesion. It was concluded that the second patient had cardiac amyloidosis because of the combination of a plasmacytoma, a bilateral carpal tunnel syndrome, intractable congestive heart failure, and a picture resembling constrictive pericarditis.

Generalized amyloidosis does not have clinical characteristics which are pathognomonic (7), but should be considered in any patient with heart failure in whom one of the common causes of cardiac disease cannot be readily established (8). Often the clue to correct diagnosis is the presence of multisystem disease. Occasionally a striking physical finding may be of aid, such as macroglossia, juxta-arteriolar deposits in the ocular fundi, or vitreous opacities.

Routine laboratory tests may show abnormal findings but are nonspecific. The intravenous Congo red test (9) is most frequently positive in the secondary form of the disease where extensive hepatic involvement is more commonly encountered. Gingival biopsy is of greatest value in the primary form and in amyloidosis associated with myeloma. Histological examination after open or needle biopsy is the only specific diagnostic test. Fluorescent staining with thioflavin T may prove especially useful for such specimens (10).

The severity of the usual signs and symptoms of heart disease when that organ is infiltrated in generalized amyloidosis depends upon the extent of cardiac deposition. When significantly involved, the heart is concentrically enlarged, heavy, and has waxy rigidity. The amyloid may be diffuse or focal, occurring as yellow to gray translucent areas within pericardium, myocardium, endocardium, or valves. The deposits often surround myofibrils. Deposition within coronary vessels with decrease in lumen or thrombosis is infrequent. Gross infarction is rare (11).

The impression that cardiac amyloidosis is present in a patient who otherwise is known to have amyloidosis, or is suspected to have it, is strengthened by three observations. First, congestive failure which is intractable to even vigorous treatment has been frequently noted (12). Myocardial involvement is responsible for most of the observed hemodynamic effects, but valvular or pulmonary infiltration may, on occasion, be important.

Second, a syndrome resembling chronic constrictive pericarditis may be seen (13, 14). There may be a history of dyspnea without orthopnea. Physical findings may include a normal-sized or enlarged heart, systolic retraction parasternally, distant heart tones, protodiastolic extra sound, high venous pressure with dilated neck veins, hypotension and narrow pulse pressure, paradoxical pulse, atrial fibrillation, enlarged and tender liver, ascites and peripheral edema, and cyanosis. Cardiac pulsations of low magnitude may be seen on fluoroscopy. On cardiac catheterization the curves reflect restriction of normal ventricular filling. The end diastolic pressure is characteristically increased to more than a third of the peak systolic pressure, and there is a high, right ventricular diastolic pressure plateau with an early diastolic dip.

Third, an abnormal electrocardiogram is common, but the changes are nonspecific (15). Characteristically, QRS complexes are of low voltage and are occasionally notched or prolonged. In the precordial leads there may be loss of R wave in the transitional zone suggestive of old anteroseptal infarction. Inverted, diphasic, or low T waves may be seen in the standard leads and in

the left precordial leads. Atrioventricular block and disordered rhythm, especially atrial fibrillation, are frequently seen.

In addition to these findings, sensitivity to digitalis was seen in the two patients presented. It is thought that this was a direct result of amyloid deposition within the heart. The occurrence of heart block or arrhythmia with relatively small doses of digitalis has been described in hypokalemia, "advanced heart disease," "severe myocardial damage" (16), viral myocarditis (17), and endocardial fibroelastosis. Experience indicates that sensitivity is not present in all patients with cardiac amyloidosis or even in the majority. However, in suspected cases it would seem desirable to undertake digitalization with even more caution than usual. Likewise cardiac amyloidosis might be suspected if digitalis sensitivity is manifested in a case of unexplained heart disease.

Summary

The clinical and pathologic features of two cases of generalized amyloidosis, one primary and the other secondary to plasmacytoma, are presented in detail with particular emphasis on amyloidosis as it involves the heart. Three clinical features resulting from this particular site of amyloid deposition are reviewed, and digitalis sensitivity is tentatively proposed as a fourth observation of possible diagnostic merit.

Acknowledgment

Appreciation is extended for review of the manuscript to Drs. John M. Weller and Muriel C. Meyers, especially in relation to the first and second cases respectively; and to Dr. C. W. Castor of the Arthritis Unit, Dr. W. S. Wilson of the Heart Station, and Dr. A. J. French, Professor of Pathology.

Summario in Interlingua

Es presentate detaliatement le aspectos clinic de duo casos de generalisate amyloidosis, con attention particular prestate al constatationes cardiac.

Un masculo de racia blanc de 58 annos de etate esseva hospitalisate a causa de intense jalnesse e congestive disfallimento cardiac. Le essayo de effectuar digitalisation ante un exploration abdominal a objectivo diagnostic esseva complicate per un extreme sensibilitate pro le droga, manifestate primarimente in arrhythmia. Le patiente moriva post le operation. Le necropsia revelava extense amyloidosis primari con interessamento marcate del corde.

Un feminina de racia blanc de 66 annos de etate esseva examinate initialmente a causa de plasmocytoma e un syndrome de tunnel carpal. Plus tarde illa esseva hospitalisate a causa de congestive disfallimento cardiac. Etiam in iste caso digitalisation produceva manifestationes de toxicitate cardiac. Le examine necroptic revelava extense amyloidosis secundari con infiltration cardiac.

Es discutite le aspectos pathologic de iste duo casos e del morbo in general. Es delineate le possibile methodos diagnostic. Emphase particular, a causa de su valor suggestive in le diagnose, es placiate super le constatation—in le examine clinic—del triade de intractabile congestive disfallimento cardiac de incognoscite etiologia, de un aspecto de ensemble resimilante chronic pericarditis constrictive, e de un electrocardiogramma anormal. In plus, sensibilitate pro digitalis es proponite tentativemente como un quarte observation de possibile merito diagnostic e etiam de signification ab le puncto de vista therapeutic.

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On the Pathogenesis of Diabetic Steatorrhea

S. M. SUMI, M.D., and J. M. FINLAY, M.D., F.R.C.P. (C), F.A.C.P.
Toronto, Canada

THE SYSTEMIC COMPLICATIONS of diabetes mellitus have been well described in the past (1). Intermittent, continuous, or nocturnal diarrhea, and nocturnal fecal incontinence have been noted frequently (1–4), and usually have been related to autonomic nervous system disorder. The complication of steatorrhea has had much less attention until recently.

Many etiological factors have been suggested to explain these gastrointestinal findings in the past. Vitamin deficiency, particularly of the B group, has been suggested by some (3), based on their success in treatment of the condition with vitamin B_{12} and liver extract. It is generally agreed that deficiency of external pancreatic secretion does not appear to be responsible (2, 4–6). Berge, Wollaeger, Scholz, Rooke, and Sprague (5) found pancreatin appeared to aggravate, rather than improve, the steatorrhea in their cases.

Most cases of diabetic diarrhea and steatorrhea have been associated with clinical evidence of autonomic neuropathy, such as decreased sweating, postural hypotension, impotence, and bladder dysfunction. Roentgenologic studies (5, 7–9) in many of these patients have shown abnormalities in gastrointestinal motility. The commonest findings have been delayed gastric emptying, either prolonged or rapid transit time through small bowel, and segmentation of the barium column. In six patients with diabetic neuropathy Kassanders (8) found that gastric retention appeared to be due to inadequate gastric contractions and not to pyloric spasm. In fact, the pylorus was patulous and barium could be forced passively into the duodenum by pressure on the epigastrium. He believed that autonomic neuropathy, secondary to diabetes, caused the disturbed gastric physiology, and noted that the finding was more frequent in diabetes of shorter duration (three to 12 years), which had been treated by long-acting insulins.

In the absence of pancreatic enzyme deficiency, the steatorrhea associated with diabetes also has been ascribed by most authors to autonomic neuropathy (5, 6, 9). A pathogenic relationship has not been satisfactorily established, although rapid small bowel transit time has been suggested as a cause of the intestinal malabsorption (6). Berge et al. (5) mention the presence of steatorrhea in two patients in whom there was no evidence of diabetic neuropathy but note that early asymptomatic autonomic neuropathy could not be excluded. The similarity in clinical features between diabetic diarrhea and the gastrointestinal disturbances sometimes following bilateral sympathectomy has been alluded to by others (4).

In a recent report concerning a diabetic patient with steatorrhea, eight unsuccessful attempts had been made to biopsy the jejunum,

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Requests for reprints should be addressed to John M. Finlay, M.D., Suite 430, Medical Arts Building, Toronto 5, Ontario, Canada.

using an oral biopsy tube (10). We have experienced the same difficulty in small bowel intubation for biopsy purposes in many of our patients with diabetes. We believe that this difficulty is more related to the neuropathic gastrointestinal dysfunction than to technique.

Recently Malins and French (4), during investigation of patients suffering from diabetic diarrhea, frequently noted unusual colonic flora in stool cultures, and found that many of these patients were relieved of diarrhea by the oral administration of antibiotics. They suggested that this abnormality of colonic bacterial flora might also be of importance in the pathogenesis of diabetic diarrhea and the intermittent steatorrhea of diabetes.

This paper is concerned with the study of the bacteriology of the *upper* gastrointestinal tract in a diabetic patient having proven steatorrhea. It includes observations made before, during, and after antibiotic therapy. These data suggest that alterations in upper gastrointestinal bacterial flora may play an important role in the pathogenesis of diabetic steatorrhea.

Case Report

The initial symptom noted by this previously healthy 58-year-old white male was the onset of impotence at the age of 47. Two years later his bowel habits became altered and he noted the onset of intermittent diarrhea lasting one to two days, followed by intervals of one to two weeks of constipation.

He was first seen in hospital at the age of 51, complaining of a two-year history of burning and coldness in both feet. Diabetes mellitus was recognized and this was controlled easily with 10 units of protamine zinc insulin daily. By the time of hospital discharge it was found that dietary control alone was sufficient.

One year later he was re-admitted with an ulcer on his right foot, and at this time 10 units of protamine zinc insulin were added to his dietary treatment. Again, control was rapidly established. At this time his diarrhea was investigated with stool cultures, gastrointestinal series, small bowel motor meal, and barium enema. All were reported to be normal except for slight delay in gastric emptying.

In the subsequent six years, his insulin requirement gradually increased to 25 to 35 units of protamine zinc insulin daily. During this interval he had continued to suffer periods of constipation, almost invariably followed by foul-smelling, painless diarrhea of one to two days' duration. He had noted no significant weight loss, bleeding, bruising, sore tongue, or other symptoms suggestive of malabsorption. There was nothing to suggest pancreatitis in his past history.

On examination he was found to have generalized dryness and scaling of the skin, associated with defective sweating. A small capillary aneurysm was noted in the left fundus and several aneurysms and a patch of exudate in the right fundus. When he was free of diarrhea, his blood pressure was 190/95 mm Hg lying down and 110/70 standing, with slight hypotensive symptoms. During an episode of diarrhea, extreme fatigue and faintness were present. His blood pressure, lying down, was 180/70 mm Hg. When he stood it was 80/40 and was accompanied by marked hypotensive symptoms.

Neurological examination showed evidence of peripheral neuropathy, most marked in the legs. There was marked wasting of the muscles of both feet with weakness of dorsiflexion. The skin was dry with evidence of defective sweating. Vibration sense was absent below the knees in both legs. No deep tendon reflexes were elicited in the arms or legs.

Laboratory investigation revealed a hemoglobin of 14.1 g/100 ml and a white count of 5,300/mm³. Total serum proteins were 6.3 g/100 ml with albumin 4.4 g/100 ml, and globulin 1.9 g/100 ml. The serum electrolytes were normal. Prothrombin time was 80% of normal. Barium meal examination showed a marked delay in gastric emptying but rapid transit through the small bowel. No abnormality was seen within the small bowel, and pancreatic calcification was absent.

He was admitted to the Metabolic Unit, where a fat balance study was performed. Chemical analysis of the stool by the method of van de Kamer and ten Bokkel Huinink (11) revealed a fecal fat excretion of 42% of ingested fat per day. The xylose tolerance test (12) was normal and 80 mEq/liter of free hydrochloric acid were found in the fasting specimen of gastric juice.

Because of previous experience with other similar patients, we studied the gastric contents bacteriologically. Culture of the fasting gastric juice yielded a heavy growth of *Str. viridans, Str. faecalis,* and *Aerobacter aerogenes.*

On the basis of the clinical and laboratory findings, and in particular, the bacterial contamination of the gastric contents, he was treated with 250 mg of chloramphenicol daily by mouth and allowed to leave hospital.

During the month subsequent to discharge he was free of diarrhea for the first time in nine years. At this time, culture of his gastric juice yielded no growth. Two months after beginning antibiotic treatment he was admitted for re-assessment of fat absorption. On the day of admission the antibiotic was discontinued. Gastric culture on the day following admission revealed *Bacillus proteus, Bacillus pyocyaneus,* and *Bacillus lactis aerogenes.* Treatment with sulphaguanidine 0.5 gm twice daily was started immediately and one week later the gastric juice was again sterile on culture. While on a fat balance study he had three loose stools, but fecal fat excretion was found to have

decreased to 7% of daily intake. Since then he has remained asymptomatic without treatment other than his diabetic regimen, even though *Escherichia coli* and *Candida albicans* were found in the gastric culture when this was re-assessed recently. Occasional brief episodes of diarrhea have recurred in recent months and the fecal fat excretion has increased to 20% of ingested fat daily.

Discussion

The association of excessive fecal fat excretion and a normal xylose tolerance test in this patient is more suggestive of a secondary than an idiopathic type of steatorrhea (12). The association of bacterial contamination of the gastric contents, diarrhea, and steatorrhea may be significant. The improvement noted in this patient's diarrhea and steatorrhea during antibiotic treatment with concomitant sterilization of the stomach may indicate a pathogenetic mechanism.

It may be that an autonomic neuropathy is responsible for disturbed gastrointestinal motility in these patients. Flaccidity of the bowel, sphincter laxity, and reverse peristalsis could result in proximal migration of coliform organisms into proximal small bowel and even into the stomach, especially during sleep when central inhibition of bowel motility is absent. That reverse peristalsis can occur has been demonstrated by the vomiting associated with gastroparesis diabeticorum. In our experience this has not been secondary to pyloric spasm. Such a situation compares favorably with the mechanism suggested by Frazer in tropical sprue (13). In the same manner, the resulting alteration in pH and enzyme activity in the small bowel may lead to a digestive defect and consequent malabsorption. This theory is also compatible with the failure of administered pancreatin to effect improvement.

Based on personal experience (unpublished), we believe it to be most unusual to find coliform organisms in gastric juice having a normal pH and a normal free hydrochloric acid content. We believe the contamination found in this patient is significant, and that it indicates some alteration in gastrointestinal motility associated with proximal migration of the colonic flora into the small bowel. In this man, contamination of the gastric contents appeared to be directly related to the steatorrhea, since oral antibiotic therapy successfully sterilized his gastric fluid and was associated with both clinical and chemical remission. It is noteworthy that this effect was accomplished with minimal doses of antibiotic agents.

Although diabetic steatorrhea rarely produces the clinical picture of malabsorption syndrome, the diarrhea may seriously interfere with diabetic control. In hospital, receiving constant diet and insulin dosage, such patients may show wide vacillations between hypoglycemia and hyperglycemia in fasting blood sugar levels. Serious cerebral damage, which we have noted in several patients, has been attributed to repeated hypoglycemic episodes. We suggest that such fluctuations in diabetic control are due in part to changes in small bowel absorption.

A number of factors are probably responsible for intestinal malabsorption in diabetes. In addition to gastrointestinal autonomic neuropathy, our findings suggest that interference with digestive processes by migration of coliform organisms into proximal small bowel may be another of the pathogenetic factors. Without doubt, other factors as yet undefined are involved, but the importance of reporting this observation lies in the simplicity of its diagnosis and its gratifying response to simple treatment.

Summary

In this report, the association of neuropathy, steatorrhea, and bacterial contamination of gastric contents is described in a male patient whose diabetes was of 11 years' duration.

Administration of small doses of antibiotic by mouth effected relief of diarrhea and steatorrhea, accompanied by sterilization of gastric cultures.

The pathogenetic implications are discussed.

Summario in Interlingua

Es reportate le caso de un masculo de racia blanc de 58 annos de etate suffrente depost 11 annos de diabete mellite. Impotentia e symptomas de neuropathia peripheric esseva presente ab le tempore del declaration del morbo. Le caso esseva characterisate per le presentia de recurrente diarrhea intermittente de novem annos de duration. In le curso del passate sex annos, le requirimentos de insulina habeva crescite gradualmente. Le examine revelava siccitate del pelle e un deficit de sudoration, anormalitates vascular in le fundos ocular, hypotension postural, e un combinate neuro-

pathia sensorio-motori le qual esseva le plus marcate in le extremitates inferior. Esseva trovate nulle evidentia de grossier anormalitate hematologic o biochimic. Un complete investigation gastrointestinal revelava nulle morbo organic capace a explicar le diarrhea. Radiogrammas del intestino tenue esseva normal. Calcification pancreatic non esseva presente. Le determination del balancia de grassia revelava steatorrhea con un excretion de 42% del ingerite grassia in le fece. Le test del tolerantia pro xylosa esseva normal. Le culturation bacteriologic del succo gastric in stato jejun revelava un grossier contamination per organismo coliforme. Le tractamento consisteva de administrationes diurne per via oral de 250 milligrammas de chloramphenicol. Iste tractamento esseva associate con sterilisation del contento gastric, cessation del diarrhea, e un reduction del excretion fecal de grassia a 7% del quantitate ingerite diurnemente. Subsequentemente le patiente ha remanite asymptomatic sin therapia additional. Ille ha mantenite su reducite excretion de grassia fecal.

Es postulate que un neuropathia autonome pote inducer un disturbation del motilitate gastrointestinal in tal patientes. Secundarimente a isto, laxitate sphincteric e un peristalse revertite permitterea alora le migration proximal de organismos coliforme ad in le intestino tenue proximal e ad in le stomacho. Le resultante alteration del pH e del activitate enzymatic in le intestino tenue poterea alora esser le base del disveloppamento de un defecto digestive con malabsorption consequente. Le autores opina que numerose factores es probabilemente responsabile pro le malabsorption intestinal, sed illes suggere que le presente mechanismo pote ben esser un del factores pathogenetic in le production de steatorrhea diabetic. Le importantia de iste these jace in le simplicitate del diagnose e del tractamento que es suggerite per illo.

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Erratum

In the paper entitled "Hypoparathyroidism Following Radioactive Iodine Therapy for Intractable Angina Pectoris," by James D. Townsend, which appeared in the *Annals of Internal Medicine* 55: 662 (October), 1961, the dosage of I^{131} was given incorrectly in microcuries (μc) instead of in the true units of millicuries (mc) throughout the case report and the discussion.

Functioning Islet Cell Adenoma with a Note about Leucine Sensitivity

A. Evan Overstreet, M.D., and Joseph J. Rupp, M.D., F.A.C.P.
Philadelphia, Pennsylvania

The occurrence of hypoglycemia as a result of excessive insulin production by islet cell tumors of the pancreas is well documented (1, 2). However, the demonstration of the tumor preoperatively is difficult since the pancreatic lesion is usually small and rarely produces symptoms because of its position. Nor do lowered blood sugar levels necessarily mean functioning islet cell tumor, inasmuch as hypoglycemia is a manifestation of diseases such as adrenal insufficiency, pituitary failure, or some large sarcomas (3) and also occurs in the absence of demonstrable lesions in children with idiopathic hypoglycemia (4), in adults with functional hypoglycemia (5), and in those who develop hypoglycemia in association with the use of tobacco (6). Furthermore, neither the severity of the symptoms nor the amount of depression of the blood sugar is indicative of the presence of islet cell tumor, since only a mild hypoglycemic syndrome occurs in some instances of pancreatic tumor, and severe syndromes may be found in the other diseases mentioned. For these reasons the diagnosis of functioning pancreatic islet cell tumor as a cause of hypoglycemia is often one of exclusion. Because of the problems associated with the diagnosis of islet cell tumor prior to operation we thought it worth-while to report the studies of two confirmed cases, each of whom had been tested for leucine sensitivity. Leucine sensitivity—the occurrence of hypoglycemia following ingestion of leucine—has been demonstrated in some cases of idiopathic hypoglycemia of childhood (7) and of functioning islet cell tumor (8); for the purpose of evaluating the response in cases of tumor we tested the procedure in the two patients reported below.

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From the Department of Medicine and the Division of Endocrine and Cancer Research, The Jefferson Medical College of Philadelphia, 1025 Walnut Street, Philadelphia 7, Pennsylvania.

Requests for reprints should be addressed to Joseph J. Rupp, M.D., The Jefferson Medical College of Philadelphia, 1025 Walnut Street, Philadelphia 7, Pennsylvania.

Case Reports

case 1

A 61-year-old white retired laborer was well until April 1944 at which time he had a generalized convulsion and was admitted to another hospital. The studies at that time included a normal skull roentgenogram, normal spinal fluid analysis, and three blood sugar determinations reported as 71, 87, and 51 mg/100 ml. Shortly after admission the patient became abusive, withdrawn, and uncooperative and was therefore transferred to the psychiatric service where he remained for three weeks. In December 1944 he had another seizure and was hospitalized again; all studies, including two blood sugar determinations, were normal. Following his discharge the seizures increased in frequency and severity, now occurring one to four times weekly; however he was not hospitalized until August 1958 when the seizure was followed by coma of 20 hours' duration. At this time the blood sugar was 38 mg/100 ml, and he promptly responded to an intravenous infusion of glucose. During hospitalization his fasting blood sugars were often as low as 40 mg/100 ml. In September 1958 he was transferred to the Jefferson Medical College Hospital.

Physical examination on admission revealed a well-oriented male who had but little memory for the details of his illness. However, his family stated that the attacks usually occurred about 11:00 AM, and the initial finding was ataxia, which was followed by decreased response to verbal stimuli, by muscular twitchings, generalized convulsions, and coma. His family noted that the attacks could be aborted if he was forced to eat when the ataxia appeared; they also noted that exercise often precipitated attacks. His weight was 152 pounds; his blood pressure varied between 130/80 and 190/110 mm Hg. The examination was negative but for a nodule in the lower pole of the right lobe of the thyroid gland.

The hemogram, urinalyses, serum cholesterol, sodium, potassium, calcium, phosphorus, lipase, and amylase were normal. Paper electrophoretic study of the plasma proteins was normal as were the tests of hepatic function including serum bilirubin, bromsulphalein excretion, thymol turbidity, and cephalin-cholesterol flocculation. Roentgenograms of the chest, skull, spine, upper and lower gastro-

intestinal tracts, cholecystogram, and intravenous pyelogram were normal. The spinal fluid pressure and analyses were normal.

The studies concerned with the blood sugar levels are detailed below. When the patient was asymptomatic the fasting blood sugar levels were often normal but sometimes as low as 36 mg/100 ml, whereas levels of 25 and 20 mg/100 ml were found when he had convulsive seizures. Values for the blood sugar during an oral glucose tolerance were: fasting, 50, one-half hour, 80, 1 hour, 85, 2 hours, 138, 3 hours, 92, 4 hours, 89, 5 hours, 53, and 6 hours, 50. After 20 hours of fast a seizure occurred, the blood sugar level was 30 mg/100 ml, and infusion of glucose resulted in complete relief. Serum levels for insulin-like activity at this time revealed a level of 1,000 μU/ml (normal value, less than 300 μU/ml).

In an attempt to assess the effects of adrenocortical steroids on the occurrence of hypoglycemia the following procedure was carried out. After the evening meal the patient was given an intravenous injection of 100 mg of hydrocortisone and 50 mg of cortisone intramuscularly, the intramuscular injection being repeated every six hours for two additional doses. Three hours after the last injection of adrenocortical steroid and 15 hours after the last meal the fasting blood sugar was 36 and remained at this level four hours more. With these conditions the steroid in the dose did not maintain the blood sugar at normal levels but did prevent the seizures usually associated with a fast of this length.

Blood sugar level immediately before the subcutaneous injection of 10 μg of epinephrine/kg of body weight was 27, and the values at 15-minute intervals following the injection were 25, 27, 33, and 35 mg/100 ml. However, the response to glucagon differed from that of epinephrine in that the blood sugar level immediately before the intravenous injection of 20 μg of glucagon/kg body weight was 44 mg, and those determined at 15-minute intervals were 70, 70, 52, and 40 mg/100 ml indicating that glucagon could mobilize liver glycogen, but epinephrine was ineffective in the dose used. Similar observations of the effectiveness of glucagon but ineffectiveness of adrenal steroids and epinephrine in raising blood sugar levels have been reported in a case of functioning islet cell carcinoma (9).

Sensitivity to leucine was assessed in the following manner. Two and one-half hours after lunch when the blood sugar level was 61 the patient ingested 0.32 g of leucine/kg body weight (twice the dose used in children). The blood sugar levels determined every one-half hour following the leucine ingestion were 57, 52, 44, and 42 mg/100 ml. The patient was free of symptoms during the procedure. A positive response to leucine consists of lowering the blood sugar to 50% or less of the initial value within 90 minutes. The response was considered to be within the normal range and not indicative of leucine sensitivity.

The studies directed at evaluation of the function of the thyroid, parathyroid, adrenal cortex, and adrenal medulla gave results within the normal range. The protein-bound iodine was 5.4 μg/ 100 ml, basal metabolism rate was 11+, and the 24-hour accumulation of I^{131} by the thyroid gland was 24%. The 24-hour urinary excretion of metabolites of the adrenal steroids (Porter Silber chromogen) and 17-ketosteroids was normal, and the increases following the 48-hour adrenocorticotrophin test were within the normal range. The variations in blood pressure were suggestive of pheochromocytoma; however, the blood pressure response to the cold pressure test, histamine stimulation, and regitine was normal. The 24-hour urinary excretion of catechol amines was 60 μg, a normal value. As mentioned, serum calcium and phosphorus values were normal as was the 24-hour urinary excretion of calcium at a time when the calcium intake was low. The tubular reabsorption of phosphate as well as the maximal tubular reabsorption of phosphorus was normal. The normal responses to the tests of thyroid, parathyroid, adrenal cortical, and adrenal medullary function indicate that the patient probably did not have the syndrome of multiple endocrine adenomata.

At operation a 2 cm adenoma was removed from the head of the pancreas which histologically was an islet cell tumor. Immediately following surgery the blood sugar levels were elevated, but they decreased to normal by the eighth postoperative day. The patient was now able to tolerate a fast without any symptoms. The blood insulin level following a fast was now 30 μU/ml whereas prior to surgery a fast of similar length resulted in a seizure and the insulin assay revealed a level of 1,000 μU/100 ml. The patient has been free of symptoms for the past 20 months.

CASE 2

A 48-year-old housewife was admitted to The Jefferson Medical College Hospital for the first time in May 1959 with the complaint of convulsive seizures recurring during the previous three months. Examination at that time was essentially negative, as were the studies performed, including blood sugar determinations, serum calcium determination, spinal fluid analyses, carotid angiography, and pneunoencephalography. The electroencephalogram showed an abnormal pattern. She was treated with diphenylhydantoin and discharged. Because of recurring seizures of greater frequency and severity she was re-admitted in July and again in November. During each admission physical examination and laboratory studies were normal; however, while two blood sugar levels in November were normal, another was 40 mg/100 ml. Following her discharge in November the attacks increased in frequency and the patient became aware that often the symptoms occurred about 4 PM and that she could abort them if she ate. As a result she gained 35 pounds in weight. At the time of her admission in May 1960 the physical examination was essentially nor-

mal. The hemogram, urinalysis, liver function tests, serum calcium, and phosphorus were normal.

The results of the intravenous glucose tolerance test (0.5 g of glucose/kg body weight infused over a one-half hour period) were: fasting, 54, one-half hour, 460, 1 hour, 193, 2 hours, 99, 3 hours, 62, 4 hours, 52, 5 hours, 44, 6 hours, 60. After a fast of 21 hours the patient became stuporous and convulsed; the blood sugar level was 17 mg/100 ml and she responded immediately to an infusion of glucose.

Two and one-half hours after lunch the patient ingested 150 mg of l-leucine/kg body weight. The blood sugar levels at 15-minute intervals prior to the ingestion of l-leucine were 34 and 32 mg/100 ml, and those at 15-minute intervals following the l-leucine were 24, 26, 15, 9, and 5 mg/100 ml. Symptoms began 45 minutes after the start of the test, and these culminated in a seizure at 75 minutes at a time when the blood sugar was 5 mg/100 ml. Although the blood sugar levels were low prior to the start of the test, the rate and degree of lowering of the sugar following ingestion of l-leucine were the result of the amino-acid and indicate a positive response.

At surgery an islet cell adenoma 1 cm in diameter was removed from the tail of the pancreas. The postoperative course was uneventful, there was no recurrence of seizures, and random blood sugar levels varied between 98 and 110 mg/100 ml. Eight days after surgery she was fasted for 24 hours without the development of symptoms, and at the end of the fast the blood sugar level was 80 mg/100 ml. Two weeks after surgery the leucine test was repeated, again two and one-half hours after lunch, and with the same dose. Blood sugar levels before testing were 98 and 88 mg/100 ml at 15-minute intervals, and those at 15-minute intervals following the ingestion of the leucine were 128, 94, 87, 108, 108, 108, 120, and 98 mg/100 ml.

Discussion

The diagnosis of islet cell tumor was suspected in each of these patients when symptoms occurred, but in each case the levels of blood sugar were normal, probably because specimens were taken at a time when the patients were free of symptoms. However, in each instance Whipple's criteria were satisfied, inasmuch as a low blood sugar was found when symptoms were present, and infusion of glucose gave immediate and complete relief of symptoms. These cases also confirm the well-known observation that patients with islet cell tumor often are assumed to have epilepsy and organic brain disease because of personality change induced by recurring hypoglycemia.

In neither case was the fasting blood sugar usually low, nor was the intravenous glucose tolerance test more than suggestive of islet cell tumor. The most significant results which might indicate that an islet cell adenoma was responsible for the clinical syndromes were found when neither patient was able to maintain a normal blood sugar on fasting and each had a seizure during a fast of less than 24 hours.

The responses to l-leucine differed in each patient. In Case 1 leucine did not alter the blood sugar to any significant degree, the decrease in sugar being only 26%, whereas in Case 2 the decrease was 85%. The results of this procedure, while limited, indicated that leucine sensitivity was not specific for the leucine-sensitive hypoglycemia of childhood and did not rule out or admit pancreatic islet cell tumor as a cause of hypoglycemia.

The mechanism by which this amino-acid induces hypoglycemia is not known. Cochrane et al. (7) have suggested that leucine either enhances the action of insulin or stimulates insulin production in leucine-sensitive children with idiopathic hypoglycemia. DiGeorge (10) has demonstrated that l-leucine increases circulating insulin in a patient with leucine sensitivity. If leucine can increase insulin production, release, or both, as our Case 2 appears to demonstrate, then the possibility is suggested that leucine in some instances can be a direct stimulus for insulin production. The lack of response to leucine in Case 2 following the removal of the tumor indicates a relationship between the patient's being sensitive to leucine and his having a tumor.

Summary

Studies of two cases of functioning islet cell adenoma of the pancreas are presented. The most helpful finding in diagnosis was the occurrence of hypoglycemia and symptoms during a fast. Of particular interest is the observation that one patient had a marked decrease in blood sugar following leucine ingestion, whereas the other had no change in blood glucose even though the dose of leucine given was twice that given to the patient with leucine sensitivity.

Acknowledgments

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SUMMARIO IN INTERLINGUA

Es describite duo casos de hypoglycemia spontanee causate per functionante adenomas a cellulas de insula. In Caso 1, extense examines laboratorial de hepate e systema endocrin revelava nulle anormalitate. Un convulsion esseva precipitate per un jejuno de 20 horas, quando le sucro sanguinee mesurava 30 mg per 100 ml e le nivello seral de activitate insulinoide esseva elevate. Durante que glucagon elevava le nivellos del sucro sanguinee al region del norma, cortisona e epinephrina habeva nulle tal effecto. Leucina in un dosage de 0,32 g per kg de peso corporee causava un reduction per 26% in le nivellos del sucro sanguinee.

Caso 2 monstrava un convulsion post 21 horas de jejuno quando le nivello del sucro sanguinee esseva 17 mg per 100 ml. Leucina in un dosage de 0,15 g per kg de pesos corporee deprimeva le nivellos del sucro sanguinee per 85% al fin de 75 minutas. A ille tempore, convulsion occurreva. Un test a leucina post le operation esseva negative.

Le duo casos illustra le importantia de un prolongate jejuno in le establimento del diagnose de functionante tumor a cellulas de insula.

Le demonstration de sensibilitate pro leucina in Caso 2 e le absentia de un tal sensibilitate in Caso 1 indica que sensibilitate pro leucina non es specificamente characteristic de leucino-sensibile hypoglycemia del pueritia e non exclude o demonstra tumor a cellulas de insula pancreatic como un causa de hypoglycemia. Es postulate le possibilitate que in certe casos leucina pote esser un stimulo directe pro le production de insulina.

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Cortisone Responsive Hypercalcemia in Proved Hyperparathyroidism

GRANT GWINUP, M.D., and BETTYE SAYLE, M.D.
Galveston, Texas

THERE IS NO AVAILABLE ASSAY for parathyroid hormone in the serum. In the absence of such a specific determination, it is necessary to rely on nonspecific procedures to differentiate hyperparathyroidism from the other hypercalcemic states. The effect of the administration of corticosteroids on the elevated serum calcium levels is one such procedure currently applied in difficult problems of differential diagnosis. It is the purpose of this report to present an exception to previous experience with this procedure in a patient with proved hyperparathyroidism.

The hypercalcemia of sarcoidosis has con-

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From the Department of Internal Medicine, The University of Texas—Medical Branch, Galveston, Texas.

Requests for reprints should be addressed to Grant Gwinup, M.D., Department of Internal Medicine, Division of Endocrinology, Ohio State University Hospital, Columbus, Ohio.

sistently responded to steroid administration (1–4). In one case of proved sarcoidosis in which the elevated serum calcium did not return to normal when steroids were given a parathyroid adenoma was subsequently found when the neck was explored (5). Vitamin D intoxication has also regularly responded even when the administration of vitamin D has been continued (6). The hypercalcemia associated with neoplasm with or without bony metastasis may or may not be affected by corticosteroid administration. This appears to be the case also in multiple myeloma and lymphoma (7–9). Hyperparathyroidism, on the other hand, has been found to present a hypercalcemia which is consistently unresponsive to steroids, and no case is yet reported in which an effect on the elevated calcium levels was observed (5, 6). The following case presents an example of hyperparathyroidism in which the persistently elevated serum calcium levels became normal with the administration of hydrocortisone.

Case Report

A 40-year-old Latin American female presented with a chief complaint of left lower quadrant pain of 17 years' duration which had been present almost constantly and could not be related to bladder, bowel, or menstrual function. Six months previously a nephrectomy had been done for a stag horn calculus of the right renal pelvis discovered during investigation of the chief complaint. There was mild constipation but no dyspepsia, no polyuria, and only questionable generalized weakness.

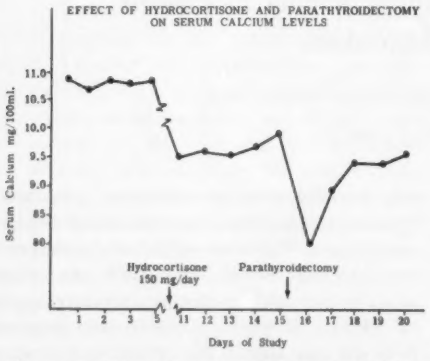

Figure 1. Elevated serum calcium levels fell to within the normal range with hydrocortisone administration. Following parathyroidectomy, temporary hypocalcemia was followed by a return to normal levels.

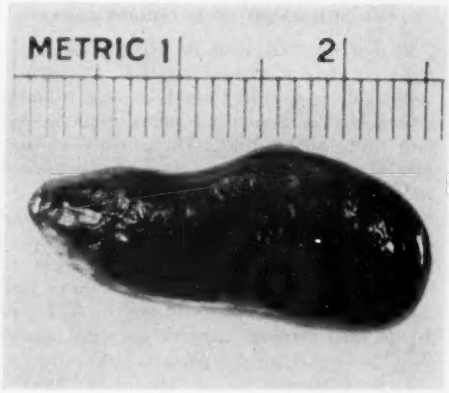

Figure 2. Tumor attached to the inferior portion of the right lower pole of the thyroid gland.

There was no history of vitamin D ingestion and no symptoms suggesting sarcoidosis.

The patient was a mildly obese Latin American female in no distress. Blood pressure was 140/90 mm Hg, pulse 72, respirations 16. Examination of the head, eyes, ears, nose, and throat was completely negative. The thyroid gland could be felt but was not unusual, and there was no neck mass. The chest was clear. The only positive physical findings were vague left lower quadrant tenderness and a well-healed right nephrectomy scar.

X ray revealed the chest examination, barium swallow, upper gastrointestinal examination, cholecystogram, and complete skeletal survey to be negative. Hemoglobin was 13.3 g/100 ml, white blood cell count, 4,800/mm^3, with a normal differential. The urinalysis was negative with a specific gravity of 1.010 on a random specimen. On the fourth and fifth days of a diet containing 125 mg calcium, the urine contained 285 and 209 mg of calcium, respectively. Fasting blood sugar was 89 mg/100 ml, blood urea nitrogen was 9 mg/100 ml, phenolsulfonphthalein excretion was 30% in 15 minutes, and total serum protein was 7.2 g/100 ml, with a normal electrophoretic pattern.

Serum calcium levels were consistently above the normal range of 9.2 to 10.5 of our laboratory (Figure 1), and serum phosphorus levels ranged from slightly low to normal with no significant change throughout the period of observation. Following the administration of 50 mg of hydrocortisone every eight hours for five days, the serum calcium levels were consistently normal. At operation a 2.5 by 1 cm pedunculated tumor was found attached to the inferior portion of the right lower pole of the thyroid gland (Figure 2). On microscopic examination this proved to be a parathyroid adenoma (Figure 3). Following operation the serum calcium levels remained at subnormal levels for several days but then returned to normal.

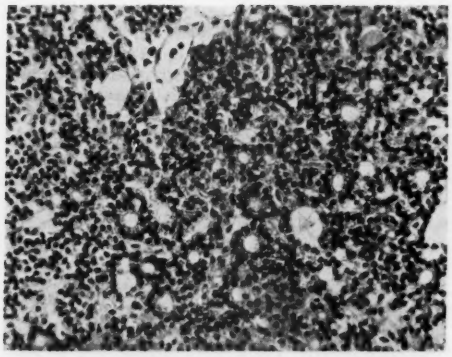

FIGURE 3. Microscopic picture of parathyroid adenoma showing predominant chief cells with no prominent fat.

DISCUSSION

In this case of proved parathyroid adenoma there was a most significant change in the serum calcium levels following five days of hydrocortisone administration. There was no clinical or laboratory evidence to suggest an additional cause of the hypercalcemia.

It is felt that variation in the laboratory determination was excluded by carefully controlling the procedure. The serum calcium values were determined by the method of Williams and Moser using the autoanalyzer (10). The serum was dialyzed into an aqueous ammonium purpurate solution following the addition of hiamine reagent and the color was measured at 550 millimicrons using a flow cuvette and a 6 millimeter light patch. Calcium carbonate standards remained the same throughout the observation period. The patient's serum calcium levels were also compared at each determination with duplicate samples from the same pool of normal serum with a predetermined calcium level of 10.1 milligrams per 100 milliliters.

It is known that the elevated calcium levels of hyperparathyroidism may occasionally show appreciable variation, and a spontaneous return to normal levels coincident with the period of hydrocortisone administration cannot be ruled out in this case; however, there was remarkable constancy of the elevated calcium before hydrocortisone was given and a suggestion of return toward those levels after hydrocortisone was discontinued.

In sarcoidosis and vitamin D intoxication, it is felt that the steroids act primarily by modifying the gastrointestinal absorption of calcium (5, 11). In malignancies, a direct action upon the neoplastic cells has been presumed (7). The mechanism by which hypercalcemia was restored to normal levels in this case of hyperparathyroidism must remain speculative; however, there is evidence implicating the influence of adrenal steroids on the action of parathyroid hormone both on the bone and at the renal level (12, 13). The question why this case responded to the calcium lowering effect of steroids, while other cases of hyperparathyroidism reported have not responded, must remain unanswered.

The purpose of this report is not to imply that no additional information can be obtained by the administration of steroids in the various hypercalcemic states, but rather to point out that as with most other diagnostic procedures there may be exceptions to the expected result. Only continued experience with this particular procedure will determine how statistically important such exceptions will prove to be.

SUMMARY

A report is presented in which the hypercalcemia secondary to a proved parathyroid adenoma promptly fell to within normal limits with the administration of therapeutic doses of hydrocortisone. This case represents an exception to previous experience in which no instance of hypercalcemia due to hyperparathyroidism has been reported to fail with steroid administration.

SUMMARIO IN INTERLINGUA

Le responsa del elevate nivellos seral de calcium al administration de corticosteroides ha essite usate como adjuta in le differentiation de hyperparathyroidismo ab altere statos de hypercalciemia. Le hypercalciemia de sarcoidosis e de intoxication per vitamina D ha respondite uniformemente. In casos de neoplasma metastatic, myeloma multiple, e lymphoma, le responsa ha essite variabile. Tamen, se trova reportate nulle caso de hyperparathyroidismo in que le elevate nivellos seral de calcium respondeva al administration de steroide.

In le presente studio, un patiente—in qui il esseva demonstrate subsequentemente que ille habeva un adenoma parathyroidic—manifestava un prompte renormalisation del elevate nivello

seral de calcium in coincidentia con le administration de hydrocortisona in un dosage de 15 mg a intervallos de octo horas durante un periodo de cinque dies.

Ante le administration de hydrocortisona, le nivellos seral de calcium variava inter 10,5 e 11 mg per 100 ml. (In nostre laboratorio, 10,5 mg per 100 ml es reguardate como le maximo ancora normal.) Subsequentemente le nivellos seral de calcium variava inter 9,4 e 9,9 mg per 100 ml, usque post le ablation del adenoma parathyroide, quando illos esseva 8,0 mg per 100 ml le prime die post-operatori e retornava al norma intra cinque dies.

Le valores del calcium seral esseva determinate secundo le methodo de Williams e Moser. Le standards de carbonato de calcium remaneva le mesmes durante le integre periodo de observation. Le sero del patiente esseva comparate a omne determination con duplicate specimens ab reservoirs multidonatori de sero normal.

Nulle evidentia clinic o laboratorial esseva detegite que poteva suggerer un causa pro le hypercalciemia altere que le hyperparathyroidismo. Ben que un spontanee retorno del elevate nivello seral de calcium al region normal, occurrente in coincidentia con le administration de hydrocortisona, non pote esser excludite, le presente caso es exceptional in tanto que passate experientias poteva esser interpretate como indication que un renormalisation de elevate nivellos seral de calcium sub le effecto de un administration de steroides non pote occurrer in casos de hyp rparathyroidismo.

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Papilledema Associated with Blood Loss Anemia

Jules R. Schwaber, M.D., and Arnold G. Blumberg, M.D., F.A.C.P.

New Hyde Park, New York

The occurrence of papilledema with severe anemia is a very rare phenomenon. Despite the high incidence of iron-deficiency anemias of all etiologies, the literature covering the past 50 years cites only 12 cases of papilledema related to anemia alone (1). It is our purpose to report a case of papilledema related to chronic blood-loss anemia which was completely reversed by correction of the anemia.

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From the Division of Medicine, Long Island Jewish Hospital, New Hyde Park, New York.

Requests for reprints should be addressed to Arnold G. Blumberg, M.D., Hillside Hospital, Glen Oaks, New York.

Case Report

A 29-year-old married Negro female was admitted to the hospital complaining of headache,

dizziness, and fatigue of two weeks' duration. Two days prior to admission, she noted double vision on lateral gaze and marked dyspnea on exertion.

Two years prior to admission, she had consulted a gynecologist because of menorrhagia. A left adnexal mass was noted on pelvic examination and surgery was advised but refused. She continued to have heavy menstrual bleeding at intervals of about 25 days. She was menstruating at the time of this admission.

She reported no impairment of mental function, no sensory loss, nor any weakness of the extremities. She denied recent exposure to toxins or pharmaceuticals other than salicylates. She remained overweight despite a 20-pound voluntary weight loss in the year prior to admission. Review of systems failed to disclose any source of blood loss other than by menorrhagia. The family history was negative for sicklemia and neurologic disease.

Physical examination revealed an afebrile, well-nourished pallid woman who appeared chronically ill. The conjunctival membranes were pale. There was abduction paresis of the left eye with diplopia on left lateral gaze. Ophthalmoscopy revealed bilateral papilledema with a marked retinal sheen and venous engorgement bilaterally (Figure 1). There were several punctate fresh perineural hemorrhages in both eyes. Visual acuity was grossly normal. Examination of the visual fields revealed an enlargement of the blind spot in each eye but no quadrant defect nor peripheral field constriction. The lung fields were clear to auscultation. The pulse was regular at 90/minute and the blood pressure was 110/80 mm Hg in both arms. A soft basal systolic murmur and slight splitting of the second sound were present. There was no cyanosis or clubbing of the fingers. The abdomen was nontender, soft, and free of masses or palpably enlarged viscera. Orientation, memory, and ability to calculate were intact. There were no sensory abnormalities. Motor power of the extremities was unimpaired. Deep tendon reflexes were hypotonic throughout, and no pathological reflexes were elicited. The uterus was enlarged to the equivalent size of a four-week gestation. A 7 cm firm, movable left adnexal mass was palpable against the left pelvic wall, and a 5 cm firm right adnexal mass was felt within the cul de sac.

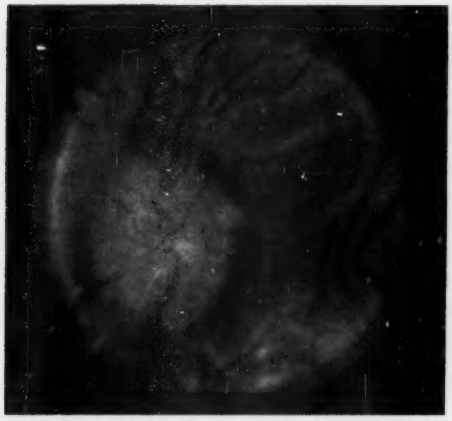

FIGURE 1. Photograph of ocular fundus of left eye taken prior to surgery shows marked papilledema and engorgement of vessels.

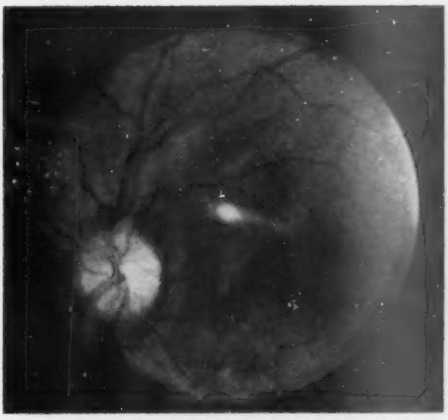

FIGURE 2. Photograph of ocular fundus of left eye taken four months after surgery showing complete disappearance of papilledema.

Urinalysis, including tests for bile and urobilinogen, was normal. The peripheral blood hemoglobin was 4.5 g/100 ml; microhematocrit, 15%; erythrocyte count, 2.32 million; leukocyte count, 7,900; reticulocyte count, 5.6%. Peripheral blood smear revealed a normal differential white count, hypochromia with slight poikilocytosis and anisocytosis of erythrocytes, and adequate platelets. There was mild basophilic stippling. Clotting time and clot retraction were normal. A sickle cell preparation was negative. Serum iron was 36 μg/100 ml. Blood chemistries, including bilirubin and prothrombin time, were normal. A serological test for syphilis was negative. Lumbar puncture revealed an opening cerebrospinal fluid pressure of 260 mm water with normal response to jugular compression. Clear, colorless fluid was obtained containing two red blood cells/mm^3, and no white blood cells. The spinal fluid protein was 21 mg/100 ml, and glucose was 74 mg/100 ml. Serology was negative. Cultures for aerobes and anaerobes revealed no growth. The colloidal gold curve was 0123320000. An electroencephalogram taken the day after admission was interpreted as an abnormal record showing diffuse dysfunction accentuated in the right posterior temporal occipital area. Chest X ray and electrocardiogram were normal. A cerebral radioisotope scan following the intravenous administration of radioactive iodinated human serum albumin revealed no abnormal cerebral concentration of radioactivity.

Course in Hospital: With bed rest and gradual transfusion of whole blood, the hemoglobin rose to 14.8 g/100 ml, and the patient's symptoms subsided. A uterine curettage was performed with four-

quadrant cervical biopsy. Pathologic specimens revealed secretory endometrium and mild chronic cervicitis. Following this procedure fresh hemorrhages were noted in both fundi, and an exudate was visible beneath the right papilla. The retinal veins appeared to be more engorged than before, and the papilledema had increased. Her neurological status remained stable, however, and a repeat electroencephalogram was interpreted as normal. A spinal tap was repeated; the fluid was clear with opening pressure of 230 mm water. Two days later the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. The pathologic report described myomata uteri, chronic cervicitis, right ovarian cyst, left parovarian cyst, and bilateral salpingitis. Her postoperative recovery was uneventful except for a mild urinary tract infection which responded readily to antibiotics. Her hemoglobin remained stable at 14 g/100 ml, and five days postoperatively the papilledema appeared to be waning. Diplopia was absent at this time. She was discharged one week later to the care of her physician. Examination of the fundi four months later revealed them to be completely normal (Figure 2), and visual acuity was 20/20 in both eyes.

Discussion

In the presence of elevated cerebrospinal fluid pressure, papilledema is generally thought to be produced by mechanical compression of the central retinal vein as it crosses the optic perineural space. The optic perineural sheath is an evagination of the intracranial arachnoid membrane. Cerebrospinal fluid pressure, therefore, is readily transmitted from the subarachnoid space to the space surrounding the optic nerve. The thin-walled central retinal vein is more readily compressed by fluid pressure elevation than is its companion artery. The resultant impediment to venous outflow from the retina can be noted opthalmoscopically as venous engorgement. As the process develops, edema of the nerve head becomes obvious. The full-blown picture frequently includes retinal hemorrhages, exudates, and macular star formation, and culminates in optic atrophy if decompression is not achieved (2–4).

Papilledema may also occur in the presence of normal intrathecal pressure. In cases of eye trauma and following intraocular surgery, it has been explained on the basis of lowered intraocular tension. Obstruction to orbital venous drainage has been implicated in cases of dural sinus thrombosis and orbital space-occupying lesions. Papilledema with normal intracranial pressure has been described in association with malignant hypertension (5), Guillain-Barré syndrome (6), sinusitis (7), cranial trauma, and in a few of the many reported cases of pseudotumor cerebri (8). It has been explained as being the ophthalmoscopic manifestation of cerebral edema, the edema being either localized to the optic chiasm and its radiations, or insufficient in degree to cause significant elevation of cerebrospinal fluid pressure. Such varied etiologic mechanisms as cerebral anoxia, hypercapnea, electrolyte disturbances, toxic-metabolic processes, and vasomotor phenomena have been invoked to explain the development of cerebral edema (1, 9, 10).

The association of papilledema and blood dyscrasia has been described in cases of thrombocytopenic purpura (11), polycythemia vera (12), pernicious anemia (13), and leukemia (4). Several reports have documented the presence of papilledema and elevated intracranial pressure in cases of iron-deficiency anemia in menstruating females [chlorosis] (1, 14). The recent case report by Lubeck (1) of papilledema and iron-deficiency anemia in a 14-year-old girl with menometrorrhagia closely parallels that of the patient described here. Both patients complained of fatigue and visual blurring; in both, the correction of anemia resulted in the return of intrathecal pressure to normal and gradual disappearance of papilledema. Watkins et al. (11) described papilledema secondary to blood loss in a male patient, following severe hemorrhage from a gastric ulcer. In their patient, the hemoglobin dropped to 6.6 g/100 ml, and spinal fluid pressure was 400 mm water. It would appear from these cases that anemia in some way evokes an increase in intracranial pressure which manifests itself clinically by papilledema. Why the anemic state is accompanied by this response in so few cases remains unexplained. Cerebral and retinal cell metabolism may be disturbed by the consequent anoxia, or as Beutler (15) suggests, by iron deficiency itself, interfering with cellular enzyme systems. It is of interest in this regard that the electroencephalographic pattern reverted to normal in our patient following correction of her anemia, before any improvement in the papilledema was apparent. Glew, Kearns, Rucker, and Essex (10, 16) noted in experimental production of papilledema in monkeys, and in clinical patient studies, that at the same level of intracranial

pressure papilledema develops in some cases and fails to develop in others. Altered pressure ratios between retinal arterial diastolic and venous pressure, and between cerebrospinal fluid pressure and intraocular pressure (17), have been considered as explanations for this seeming paradox, implying that papilledema occurs when local compensatory mechanisms are overwhelmed.

It is important to note that papilledema is not always a herald of neoplasia [only 51% of 70 cases in the series of Korein, Cravioto, and Leicach were associated with brain tumor] (18). Papilledema is not always associated with increased cerebrospinal fluid pressure (19). It does occur in anemic states, but why it occurs in relatively few anemic patients and by what mechanism it occurs are questions that remain largely unanswered.

Summary

A case of papilledema in the presence of increased cerebrospinal fluid pressure in a patient with blood loss anemia secondary to menorrhagia is reported. The pathogenesis of papilledema is considered with reference to its presence in anemic states.

Summario in Interlingua

Es describite le caso de un femina de 29 annos de etate qui se presentava con le symptomas de cephalalgia, vertigine, e fatiga. Le examine revelava marcate grados de papilledema con congestion venose e hemorrhagias punctuate in le fundos del oculos. Le utero esseva allargate, e massas adnexe esseva presente bilateralmente. Al tempore del hospitalisation le hemoglobina esseva 4,5 g per 100 ml. Le hematocrite esseva 15%, le numeration erythrocytic 2,32 milliones, e le procentage de reticulocytos 5,6. Un punctura spinal revelava un pression de 260 mm de aqua, con un concentration de proteina de 21 mg per 100 ml. Un electroencephalogramma monstrava dysfunction diffuse. Le patiente esseva tractate con transfusiones e postea subjicite a un total hysterectomia abdominal con salpingo-oophorectomia bilateral. Le reporto pathologic describeva myomas de utero, cervicitis chronic, cystes ovarian, e salpingitis bilateral. Studios catamnestic revelava le complete resolution del papilledema e le complete disparition de omne le symptomas. Le electroencephalogramma revertava al norma. Le caso es presentate como exemplo de papilledema producite per anemia e curate per le correction del anemia e le ablation del causa del anemia.

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Hemocholecyst

A Neglected Cause of Gastrointestinal Hemorrhage

THOMAS J. FITZPATRICK, M.D., F.A.C.P., *Joliet, Illinois*

HEMOCHOLECYST IS DEFINED AS HEMORRHAGE from the gall bladder which is nontraumatic in origin and which has not resulted from intraperitoneal rupture of the gall bladder (1).

The purpose of this paper is to review the world literature bearing on this subject, and to report an additional case, more unusual in that the hemocholecyst was associated with a cholecystogastric fistula.

Most cases of hemocholecyst are diagnosed at surgery or on post-mortem examination. Clinically they are classifiable in large series of massive gastrointestinal hemorrhages as the 2 to 5% of cases of hemorrhage from undetermined source, unknown etiology, or unusual and unexpected causes of hemorrhage.

Most authorities (2, 3) are agreed that 85 to 90% of massive upper gastrointestinal hemorrhages are caused by gastrointestinal ulceration, bleeding esophageal varices, or gastritis. Another 5% can be accounted for etiologically on the basis of malignancy of the esophagus or stomach, or bleeding from hiatus hernia. The remaining 5% of cases still constitute a challenge.

That bleeding does occur commonly in cases of gall bladder pathology is indicated by Lichtman's statement (4) that gross bleeding is evident in 1 to 5% of all these patients. Eusterman (5) found occult blood in the stool of 20% of patients with chronic gall bladder disease, while Hudson and Johnson (6) demonstrated positive tests for occult blood in the feces of 13% of 100 consecutive cases of cholelithiasis.

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From the Silver Cross Hospital, Joliet, Illinois.

Requests for reprints should be addressed to Thomas J. Fitzpatrick, M.D., 1201 Campbell Street, Joliet, Illinois.

HISTORY OF HEMOCHOLECYST

Hemocholecyst was first reported in 1892 by Naunyn (7), who described three cases of ruptured aneurysm of the hepatic or cystic artery associated with gall stones or cholecystitis. This resulted in massive hemorrhage into the gall bladder.

A few years later Huguein (8) reported a case of hemorrhage into the gall bladder and throughout the extrahepatic biliary system. This was found to have been caused by a carcinoma of the common bile duct.

In 1915 Schnyder (9) reviewed the literature of hemorrhage from the gall bladder and found reports of eight cases. He contributed two more of his own. One was a man, aged 72 years, who was found to have two ulcerations of the gall bladder (but no gall stones), producing a fatal hemorrhage that filled the intestine. In another case, severe hemorrhage from the gall bladder penetrated into the stomach through an ulceration connecting both organs.

In 1925 Heusser (10) reported the case of a 47-year-old man with cholelithiasis who developed massive hemorrhage into the lumen of the gall bladder.

Fiessinger, Bergeret, and Leveuf (11), in 1938 first applied the term "hemocholecyst" in describing hemorrhage from the gall bladder. They also applied the term "nontraumatic effusion." Their report added a total of four cases to the literature.

One year later, Meyer-May and Joyeaux (12) reported an instance of enormous hemorrhage into the gall bladder that was probably due to trauma incurred in a football game.

In 1942 Laird, Gehret, and Rigney (13) reported two cases: One had moderate anemia, positive stools for occult blood, and a history of melena; the other had anemia but no history of gastrointestinal bleeding. At operation both patients were found to have gall stones. The second case had a massive hematemesis

postoperatively. Follow-up in this case failed to reveal either further bleeding or another source for the hemorrhage. It would appear that the gall bladder as a source of the bleeding in the second case was presumed, and perhaps was even unlikely.

A rare cause of hematemesis and massive hemorrhage was recorded by Gordon-Taylor (14) in 1943. He reported the rupture of an aneurysm of the hepatic artery, with a communication between the aneurysm and the interior of the gall bladder. His search of the literature yielded seven similar cases in which erosion of such an aneurysm caused rupture into the gall bladder.

In 1946 Hudson and Johnson (6) published a review of the literature. Twenty-four cases were recorded of massive hemorrhage attributable to nontraumatic gall bladder disease. These authors contributed four cases of their own. All of these showed cholelithiasis, and one had, in addition, a sarcoma of the gall bladder.

The same year Hutchins, Manzer, and Stranahan (15) reported on a case of massive bleeding from cholecystitis glandularis proliferans, a condition variously called adenoma, polyp, cystadenoma, adenomatous polyp, papilloma, or fibroadenoma of the gall bladder. At operation, a polyp-bearing gall bladder with evidence of fresh bleeding from multiple small ulcerations surmounting the polyps was found.

Christopher and Savage in 1948 (16) reported the only case in the literature of massive hemorrhage into the gall bladder in a patient with essential hypertension. A careful examination of this gall bladder failed to reveal calculi, polyps, vascular lesions, or neoplasm. There had been no history of trauma. Rightfully or not, the authors concluded that this case represented apoplexy of the gall bladder due to the patient's hypertensive disease.

Apparently in the last decade there has been some clinical awakening to the fact that the gall bladder is, at least on occasion, a source of massive hemorrhage. More articles have been written specifically referring to this possibility. One of these reports was by Kerr, Mensh, and Gould (17) in 1950. They added a report of a patient with several bouts of melena in whom repeated X rays of the gall bladder and gastrointestinal tract were normal. Gastroscopy and liver function tests were likewise unrewarding. Subtotal gastrectomy was done, but no lesion was demonstrated, and bleeding continued. Subsequent laparotomy showed a gall bladder and bile tract filled with blood that was assumed to have been intrahepatic in origin since no lesion of the gall bladder or biliary ducts was found.

Kehrer and de Minjer (18) in 1951 presented a case report of hemorrhage into the gall bladder from a peptic ulcer of that organ. Sections of the ulcer-bearing area of the gall bladder showed typical parietal cells of heterotopic gastric mucosa. In 1955 Ivanov (19) also reported a massive hemorrhage occurring from a peptic ulcer situated in the gall bladder.

Greene, Marroquin, and Thomas (20) in 1952 reported an unusual case that had not been previously reported, where a blood-filled gall bladder was found at operation in a patient with a bleeding duodenal ulcer. A gastric resection was performed, but no lesion of the gall bladder or bile ducts was demonstrated. Subsequently the patient underwent a cholecystectomy for acute and chronic cholecystitis. The authors surmised that the blood was present in the gall bladder by reflux through an incompetent sphincter of Oddi.

In 1954 Bosch Del Marco (21) reported an unusual case of a patient who not only vomited blood but also simplified the diagnosis by orally expelling several gall stones. The patient was found at surgery to have a cholecystoduodenal fistula, and he survived subtotal gastrectomy and cholecystectomy.

Manfredi (22) in 1958 reported on a woman with hematemesis, anemia, and jaundice. At surgery the gall bladder contained stones and blood clots. The common bile duct was filled with blood.

This would bring the total number of hemocholecysts in the literature to 34. An additional case, recently encountered, is herewith presented.

Case Report

A 51-year-old white male was first seen on July 21, 1952. His present illness had begun in February, 1952, with sharp substernal pain which radiated into the abdomen, especially into the midepigastrium. At onset the pain was quite severe, and required admission to St. Joseph's Hospital in February, 1952. A review of this hospital chart disclosed the following facts: The pain was localized

FIGURE 1. Oblique view of barium-filled stomach and duodenum, demonstrating the compression deformity of the prepyloric area of the stomach. Note that there is no air or barium in the biliary tract.

in the right upper quadrant of the abdomen, and marked tenderness was elicited on pressure there. The patient gave a history of having vomited perhaps an ounce of bright red blood during the course of the pain. Intermittent fever of 101 to 102 F had been present for four days. The laboratory data disclosed a red cell count of 4.9 million; hemoglobin, 14.5 g/100 ml; white cell count, 7,600/mm^3 with a normal differential; urinalysis, normal; Kahn test, negative. X ray of the chest was reported as normal, and X ray of the gall bladder showed a nonfunctioning organ. The patient was discharged asymptomatic.

Following this hospitalization the patient had shunned medical attention, despite continuing episodes of substernal distress. His appetite had been poor, but he denied weight loss, history of jaundice, or further evidence of gastrointestinal bleeding until three days prior to the July, 1952, admission to Silver Cross Hospital, Joliet, Illinois. At this time he again suffered a hematemesis of an undisclosed and unestimated amount.

Examination showed a blood pressure of 150/88 mm Hg. There was tenderness in the right upper quadrant of the abdomen. The chest was emphysematous. Examination of the heart showed no abnormalities. Varicosities were present in the right calf.

Laboratory data were as follows: red cell count, 4.4 million; hemoglobin, 8.7 g/100 ml; white cell count, 5,250/mm^3 with a normal differential. The Kline test was negative. Bromsulphalein test showed no retention 30 minutes after injection of 2 mg/kg of the dye. Serum albumin was 3.75 g/100 ml; serum globulin, 3.1 g/100 ml; albumin:globulin ratio, 1.2:1. Urinalysis was negative. Serum bilirubin was 0.8 mg/100 ml total; alkaline phosphatase, 3.2 Bodansky units.

The tenderness in the right upper quadrant persisted but was less marked, and there was no further sign of gastrointestinal bleeding.

Fluoroscopic examination of the upper intestinal tract showed a constant deformity of the antrum of the stomach. In addition, there was a duodenal defect that appeared to be due to extrinsic factors (Figures 1 and 2). Neoplasm could not be ruled out. In view of the patient's known gall bladder disease, it was felt that the duodenal deformity could be due to adhesions between that organ and the gall bladder. Fluoroscopic examination of the colon was normal.

It was felt advisable to explore the patient surgically, in view of the known gall bladder disease;

FIGURE 2. Oblique view of stomach, showing obliteration of normal mucosal folds of distal antrum. Also note barium streaks projecting from prepyloric part of stomach, and representing fistulous tracts between stomach and gall bladder.

but perhaps more pressing was his history of hematemesis and the possibility of a gastric malignancy.

The patient was discharged to arrange his affairs, but was not seen again until October, 1952, when he presented with a history of having wakened at midnight with a severe pain in the upper abdomen. He vomited, but there was no hematemesis at this time. He fainted en route to the bathroom and passed a tarry stool. In rather taciturn fashion he admitted to the passage of tarry stools over a three-day period. He further stated that he had been gainfully employed in the interim and had even gained ten pounds in weight.

Examination at this time showed a blood pressure of 120/80 mm Hg. Diffuse tenderness was present in the upper abdomen, and a tender, irregular mass, roughly 10 by 12.5 cm in size, descended in the left upper quadrant of the abdomen with deep inspiration.

Laboratory data showed a normal urinalysis. Red cells numbered 1.85 million, and hemoglobin was 4.5 g/100 ml. White cells numbered 8,000/mm^3 with a normal differential. The patient received 1,000 ml of whole blood intravenously, following which the red cells numbered 2.2 million and hemoglobin was 5.6 g/100 ml. Temperature was 100.4 F, and tarry stool was present in the rectum.

Six hours after admission the patient suddenly vomited enormous quantities of dark and bright red blood, rapidly lapsed into a coma, and died.

The pertinent autopsy findings were as follows:

Gross: The right upper abdomen contained a hard, firm, irregular mass involving the first portion of the duodenum, the gall bladder, liver, and peritoneum.

Five hundred milliliters of clotted blood were present in the stomach. Clotted blood was present in the jejunum and ileum. The gall bladder was distended and the wall thickened. It measured 12 by 7 by 7 cm. It was incorporated by inflammatory adhesions to the stomach, duodenum, and pancreas (Figure 3).

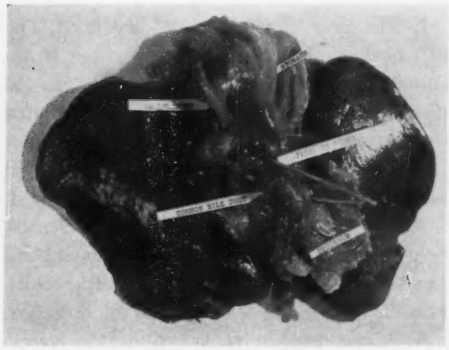

FIGURE 3. Gross specimen removed at autopsy shows mucosal surface of distal stomach and duodenum, with gall bladder attached to inferior surface of the liver. Note probe in one of the fistulous tracts in prepyloric portion of the stomach.

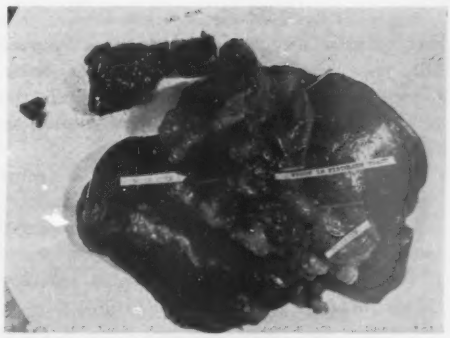

FIGURE 4. Autopsy specimen, with gall stone and blood clot removed from gall bladder. Note their relative size.

When the gall bladder was opened it was found to be filled with clotted blood, and a single 5 by 5 by 3 cm, greenish-brown stone was present (Figures 3 and 4). At the level of Hartmann's pouch a fistulous tract connected the gall bladder with the stomach. It opened into the stomach 1 cm proximal to the pylorus and consisted of three small openings. The mucosa of the stomach in this region was reddened and thickened. The common bile duct was patent but distended with some blood clots.

The first part of the duodenum was markedly constricted, and measured 4 cm in circumference. Distal to this constricted area the duodenum measured 7 cm. The mucosa of the duodenum was intact.

Microscopic: The entire wall of the stomach was infiltrated with round cells and some polymorphonuclears. The mucosa was absent in one area and was replaced by fibrous connective tissue. The mucosa of the gall bladder was ulcerated. The wall was markedly thickened with fibrous connective tissue. There was also a marked infiltration of round cells.

Autopsy diagnoses:

1. Cholecystitis with cholecystogastric fistula.
2. Massive hemorrhage through cholecystogastric fistula from ulcerated gall bladder.
3. Cholelithiasis.

COMMENT

This case presents two unusual complications of cholecystitis with cholelithiasis: the massive upper gastrointestinal hemorrhage from the gall bladder, thought by the pathologist to have been due to the erosive effect of the single gall stone on the gall bladder mucosa; and the presence of a cholecystogastric fistula.

A careful search of the literature showed that this peculiar combination has been reported only once previously: Schnyder and Lobstein reported a patient with hemorrhage from the gall bladder involved in a fistulous connection with the stomach.

This additional report brings the total number of hemocholecysts in the literature to 35.

Fistulous connections have been reported between the gall bladder and most other organs of the body, including the duodenum, stomach, colon, pleural space, and bronchi (3).

Puestow (23) quotes Barman and Rigler as finding 67 internal biliary fistulae in over 30,000 autopsies. Davison and Aries (24) found seven such fistulae in a series of 6,000 autopsies at Cook County Hospital. Tracey and McKell (25) found 21 cases of internal biliary fistula between the years 1927 and 1942 at the Lahey Clinic. (It is interesting to note that five of these were demonstrated by roentgenologic study.)

In the clinical evaluation of a patient with an internal biliary fistula, Narkin, Strauss, and Strauss (26) have made the point that the formation of a fistula may result in sudden cessation of the pain of biliary colic. Following this, fever and chills may appear as a result of the retrograde cholangitis that may develop. Weight loss of a marked degree is another common clinical finding in the patient with an internal biliary fistula.

Diversified as the multiple causes of hemocholecyst may appear to be, they may be classified as follows:

1. Gall stone.
2. Vascular:
   a. Arteriosclerosis.
   b. Aneurysm of cystic and hepatic arteries.
   c. Hypertension (?)
3. Malignancy.
4. Polyps (benign).
5. Heterotopic gastrointestinal mucosa with peptic ulceration.

Gall stone is the lesion most commonly causing or associated with hemocholecyst. This implies a mechanically irritative effect as the direct etiologic concept.

A study of causes may provide a correct diagnosis in many cases. This is especially important since most of these lesions are surgically accessible and curable.

As indicated, trauma as a cause of hemocholecyst is excluded from this discussion, but it deserves mention because of the confusion it can cause. On occasion, trauma to the abdomen may have caused bleeding into the gall bladder, but the trauma may have antedated the appearance of clinical symptoms by a period of three to six weeks. The history of trauma may be remote to the patient whose symptoms of pain or shock obviate detailed questioning, and it is overlooked as the cause.

That malignancy appears uncommonly as a cause of hemocholecyst may seem strange. However, Burdette (27) studied 61 cases of primary carcinoma of the gall bladder and found that gastrointestinal hemorrhage was rare, and that secondary anemia was not a common feature of the disease.

It was frequently noted in the literature that many patients with hemocholecyst had had much medical attention and perhaps several hemorrhages before the correct diagnosis was made. Even then, the diagnosis was most often made in the operating room or at autopsy. It is hoped that calling to mind this possibility as a cause of gastrointestinal hemorrhage may further reduce the shrinking percentage of cases diagnosed as hemorrhage from undetermined source.

Summary

1. The term "hemocholecyst" is defined. The gall bladder as a source of hemorrhage is discussed, and hemocholecyst is placed in its proper relation to other causes of gastrointestinal hemorrhage.

2. A review of the literature on this subject is presented. A total of 34 cases was found.

3. An additional case report is presented, bringing the total to 35. This case was unusual because of a coexisting cholecystogastric fistula. It is the second case of its kind in the literature.

4. A classification of hemocholecyst according to etiology is presented, based upon reports in the literature.

5. Aids in preoperative and ante-mortem diagnosis are suggested.

Acknowledgment

The author is indebted to Dr. Benjamin H. Neiman, pathologist, Silver Cross Hospital, Joliet, Illinois, for the autopsy findings in this case.

Summario in Interlingua

Le definition de hemocholecyste es: un hemorrhagia ab le vesica biliari, le qual es nontraumatic in origine e que non ha resultate ab un ruptura intraperitonee del vesica biliari.

In grande series de massive hemorrhagia, casos del presente typo se trova generalmente classificate in le gruppo del 2 a 5% de casos de hemorrhagia a origine indeterminate.

Es revistate le reportos de casos individual trovate in le litteratura del mundo. Lor numero total es 34. Un caso additional, incontrate per le autor, es reportate in detalio. Iste caso esseva additionalmente inusual in tanto que in illo un fistula cholecystogastric esseva trovate. Le patiente periva post un serie de massive hemorrhagias gastrointestinal.

Le varie factores etiologic de hemocholecyste es classificate e discutite. Calculos biliari es le causa—o le causa associate—trovate le plus communmente. Malignitate es un causa incommun.

Es discutite certe utile observationes clinic que pote render possibile le diagnose de hemocholecyste e de fistulas de vesica biliari ante le exploration operatori o le examine necroptic.

Inter 85 e 90% del massive hemorrhagias supero-gastrointestinal es causate per ulceration gastroduodenal, sanguinante varices esophagee, o gastritis. Un gruppo additional de 5% es causate per malignitate del esophago o del stomacho o representa un sanguination ab un hernia de hiato. Le remanente 5% de casos de inusual o inexpectate causas de hemorrhagia constitue un gruppo frequentemente problematic e de interesse particular. Il es in iste gruppo que le casos de hemocholecyste es incontrate.

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BRIEF COMMUNICATION

Rupture of the Normal Stomach during Oxygen Therapy by Nasal Catheter

A Brief Report of Three Cases and a Simple Means of Preventing This Disaster

ARTURO LONGOBARDI, M.D., DAVID W. RUGGLES, M.D.,
and ALEX M. BURGESS, M.D., F.A.C.P.
Providence, Rhode Island

RUPTURE OF THE NORMAL STOMACH due to sudden distention during oxygen therapy by insufflation through a nasal catheter is a rare but tragic occurrence. The patients receiving this type of treatment are, of course, suffering from a serious condition or the use of oxygen would not be indicated. The tear in the stomach or esophagus with sudden severe distention of the abdomen with oxygen and leakage of stomach contents may well be more than the ailing individual can tolerate as was the case in two of the three instances here reported. Three similar cases have recently been published (1).

When properly applied, the method of oxygen administration originally described by Wineland and Waters in 1931 (2), involves use of a well-lubricated catheter, the tip of which lies in the oropharynx. This insures the inhalation of oxygen-rich air with every inspiration whether the patient breathes through the mouth or the nose.

The method is simple and reliable but is by no means fool-proof. Leaks often occur in the system so that a patient may in fact be receiving no oxygen whatever despite the fact that there is active bubbling in the bottle used to moisten the oxygen. The catheter must be firmly fixed in position. Ordinarily a properly positioned catheter is visible just opposite the uvula. It has been routine to check its position before turning on the flow of oxygen. A flow of four to six liters per minute is well tolerated, as a rule, and results in a sufficient increase in the partial pressure of oxygen in the alveolar air so as to be therapeutically valuable where really high concentrations of oxygen are not needed.

As usually applied, the catheter, after being properly placed with its tip at the level of the tip of the uvula, is fastened to the nose or upper lip by adhesive plaster. It should be removed, cleaned, and reapplied every six to eight hours. When this is done and the catheter is reinserted and not properly fixed in position, it is quite possible for it to slip further into the nose than is intended and to enter the esophagus. The result is that the stomach is rapidly dilated with oxygen if the flow has been started. Ordinarily this is not serious, but in some instances, like those reported here, rupture of the stomach wall can occur, with disastrous results.

The three patients who have come to our attention were elderly women aged 69, 63, and 86 years. The first was suffering from epidermoid carcinoma with metastases and was given oxygen by nasal catheter after extensive axillary dissection. At the end of an hour and a half it was found that her abdomen was markedly distended and her pulse weak and irregular. She was operated upon, and there was a free escape of gas when the peritoneal cavity was entered. No perforation was found at operation, but five days later the patient died. At autopsy a "recent sealed gastric perforation" was discovered. There was no peritonitis. The tear in the mucus membrane was slit-like and 5.5 centimeters in length. It per-

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Requests for reprints should be addressed to Alex M. Burgess, M.D., 107 Bowen Street, Providence, Rhode Island.

forated the muscularis at one end, and this perforation was sealed by the lesser omentum. The tear was located about 8 centimeters from the pylorus on the greater cuvature. The autopsy also showed arteriosclerotic heart disease with old and fresh myocardial infarcts and chronic pyelonephritis with lithiasis.

The second patient, 63 years of age, received oxygen because of an acute attack which was in fact due to a massive pulmonary embolism and was so diagnosed. About two hours after the oxygen was started it was found that her abdomen was "hard and distended." She died two hours later. The cause of death was certainly the massive embolism, but a "recent laceration of the stomach wall and free gas in the abdominal cavity" were noted at postmortem. The laceration was about 4 centimeters in length and was located in the region of the greater curvature slightly nearer the pylorus than the cardia.

In the third instance, the patient, a lady of 86, was recovering in satisfactory fashion from an attack of congestive failure. Oxygen was administered by nasal catheter at 4 liters per minute. The catheter was removed when the patient was to be fed, and was reinserted afterward. A "minute or two" later she cried out with pain and became cyanotic. It was found that her abdomen was "board-like," and there was evidence of subcutaneous gas in the upper thoracic area and the neck. X rays showed an extensive pneumoperitoneum. She was operated on, and at the junction of the esophagus and stomach on the right side there was "a rent in the esophagus" at least an inch in length, and a continuation of the rent into the stomach about half an inch long. This was repaired. This patient died about 20 minutes after the completion of the operation.

These tragic episodes illustrate the danger of sudden gaseous distention of the stomach that can occur if the catheter becomes inserted too far and enters the esophagus. It is our belief that markers on the catheter that may indicate but do not prevent this deep insertion of the catheter are not a sufficient safeguard to the patient. We have, therefore, devised a catheter which has a disc attached to it which prevents the catheter from entering the nose beyond the required distance.

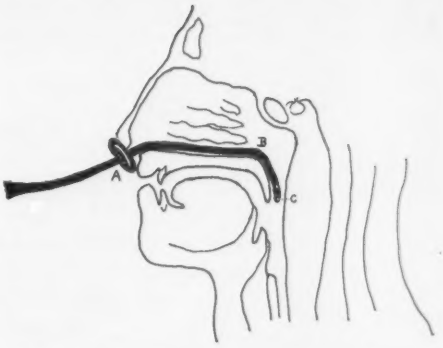

FIGURE 1. Nasopharyngeal area with catheter in place. A = disc; A-C = 12 to 14 centimeters; B-C = 3 to 3.5 centimeters.

Our studies of adults with small, average, and large heads have shown that the distance from the external nares to the tip of the uvula varies from 12 to 14 centimeters (A to C on diagram). Estimations on the cadaver indicate that the area in which the perforated tip of the catheter should lie is about 3.5 centimeters in length (B to C in diagram). Thus a catheter with the disc located 12 to 12.5 centimeters from its tip and inserted until the disc impinges on the nose and upper lip will be correctly located, and accidental intubation of the esophagus will be prevented (Figure 1). If the disc is made with the central hole small enough so that it fits tightly on the catheter, it is impossible to move it without stretching the catheter to decrease its circumference. This is preferable to having the disc cemented in position, and it allows for changing its location as needed.

We believe that the use of a catheter of this type will be the means of preventing serious consequences, such as we have described, which can result from the insertion of the catheter into the esophagus and the sudden distention of the stomach with oxygen.

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CLINICAL STAFF CONFERENCE

Tangier Disease

Combined Clinical Staff Conference at the National Institutes of Health

Moderator: DONALD S. FREDRICKSON, M.D. *Discussants:* PAUL H. ALTROCCHI, M.D., LOUIS V. AVIOLI, M.D., DE WITT S. GOODMAN, M.D., and HOWARD C. GOODMAN, M.D.
Bethesda, Maryland

DR. DONALD S. FREDRICKSON: This is the story of an island, a family, and a strange malady. In telling it we hope to acquaint you with some of the biochemical approaches to current problems in both fat transport and the lipid storage diseases. Since our story lends itself to the narrative style, we are taking advantage of this in our presentation.

In addition to those of us who have been concerned specifically with the study of an abnormality which we have termed "Tangier disease," we are fortunate to have Dr. Louis Avioli and Dr. De Witt Goodman as discussants.

Dr. Altrocchi, of the National Institute of Neurological Diseases and Blindness, will introduce today's topic.

DR. PAUL H. ALTROCCHI: We may begin with the tonsillectomy performed on a five-year-old boy, T. L., in April, 1960, at Northampton-Accomac Memorial Hospital in Nassawadox, Virginia. His tonsils were not only so huge that he was beginning to have difficulty swallowing but they were remarkable in their appearance. This is recorded in the operative notes of Dr. J. Thomas Edmonds: "The tonsils are quite yellowish-gray in appearance and there are many lobulated areas, apparently somewhat honeycombed-like in appearance, with many septi running through these yellowish-gray islands of tissue. Instead of being relatively smooth, they are somewhat wrinkled as if they were separate compartments. On removal, the adenoids had the same yellowish-gray appearance and appeared to be lobulated also."

Dr. Edmonds and his pathologist, Dr. Cecil Sinclair, sent these tonsils to the Armed Forces Institute of Pathology, (accession No. 957398). There they found many foam cells along the surface, in the septa, and extending into the lymph follicles themselves (Figure 1). Patient T. L. was then referred to the National Cancer Institute with a tentative diagnosis of Hand-Schüller-Christian disease or Niemann-Pick disease.

On his admission to the Clinical Center, physical examination was within normal limits except for moderate hepatosplenomegaly and scattered enlarged lymph nodes, especially in the neck. Neurological examination was completely normal. After biopsies of liver and lymph node failed to

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Requests for reprints should be addressed to Donald S. Fredrickson, M.D., National Heart Institute, Bethesda 14, Maryland.
A preliminary report of this disease was presented at the Symposium on Sphingolipidoses held in Brooklyn, New York, March 29, 1961 (1).

fulfill the histological criteria of Hand-Schüller-Christian disease, the patient was kindly referred to the National Heart Institute by Dr. Louis V. Avioli,* of the National Cancer Institute, with a tentative diagnosis of Niemann-Pick disease.

DR. DONALD S. FREDRICKSON: Let us discuss Niemann-Pick disease briefly at this point in order to provide a frame of reference for Tangier disease. It was described first in 1914 (2) by Niemann, a Berlin pediatrician, who observed in an infant the now typical combination of hepatomegaly, splenomegaly, and severe central nervous system dysfunction ending fatally by the second year of life. Ludwig Pick later correlated the findings in the first case with several others, and the combined eponym has persisted.

The primary finding at biopsy in Niemann-Pick disease is the presence in the tissues of large cells filled with droplets similar to those shown in Figure 1. Ten years after the first case was reported, it was discovered by Klenk in Cologne that the abnormally high concentration of lipid in these cells included an especially exaggerated amount of sphingomyelin. In addition to this lipid phosphatide, other phospholipids and cholesterol are also increased.

Niemann-Pick disease is remarkable for the degree to which its lesions are spread, a pervasiveness due to primary involvement of the reticuloendothelial system. Foam cells may be present in virtually every tissue in the body. In the nervous system destruction of ganglion cells usually occurs, with accompanying demyelination. These changes are often detectable by retinal examination in the form of a "cherry-red spot," also common to Tay-Sachs disease, and due to degeneration of fibers in the macular region. The demonstration of ganglion cell changes in intestinal tissue obtained by rectal biopsy is useful in detection of this and similar lipidoses.

FIGURE 1. Large histiocytes or foam cells present in the tissues of patient T. L. Hematoxylin-eosin stain. These cells stained heavily for lipid using oil red O.

The clinical expression of the syndrome called "Niemann-Pick disease" is today known to be quite variable. The age of detection may vary from a few weeks of life to adulthood. Wide differences in severity of neurological involvement and even in the composition of the tissue lipid accumulations also occur. Thus, it seems certain that cases now sharing this diagnosis because of similar clinical and histological findings will eventually be separated into several diseases with different biochemical bases (3).

Even considering the variability of "Niemann–Pick disease," the findings in T. L. were sufficiently unusual to make this diagnosis unlikely from the start. He had no nervous system disease, which is exceedingly rare in this disease in a patient five

* Dr. Avioli is now an Instructor in Medicine at Seton Hall College of Medicine, Jersey City, New Jersey.

years of age. Despite widespread soft tissue changes, we also failed to find foam cells in the bone marrow although this can also happen even in "classical" cases.

The histochemist is quite limited in his ability to distinguish different lipids in microscopic sections and usually cannot provide a definitive diagnosis within the "foam cell disorders." However, a combination of certain stains did provide useful clues in further pursuing the diagnosis in the present cases. Oil red O, soluble in most lipids, filled the foam cells in the lymph node and many of the parenchymal cells in the liver with an unusually bright red color. The Smith-Dietrich reaction, believed to stain mainly unsaturated fatty acids in phospholipids and often considered to be rather specific for Niemann-Pick tissues, did not stain these large foam cells significantly. The periodic acid-Schiff reaction for detecting adjacent *cis*-hydroxyl groups in substances like glycogen or polysaccharides gave only a normal faint reaction. However, the Schultz test, which is a modification on the micro-scale of the Liebermann-Burchardt reaction, gave a fleeting but brilliant blue-green color to the foam cells, suggesting high concentrations of cholesterol or some very similar sterol.

Techniques have advanced too far today to permit any move in this type of diagnostic problem short of full confirmation of histochemical impressions by quantitative lipid analyses. Hence, sufficient biopsy material, kept *frozen* and away from the lipid solvents found in all conventional fixatives, was then examined chemically for the identity of the stored lipids.

The total lipid was considerably increased in the cervical lymph node from T. L. Quite unexpected was the finding that this increase was attributable almost solely to an increase in the sterol content. As we will show later, this sterol was cholesterol; and its esters were present in amounts rarely observed. The tissue concentration of phospholipids, particularly the sphingomyelin fraction, was quite within normal limits.

At this point, then, we had a five-year-old boy with hepatosplenomegaly and large lymph nodes filled with foam cells. These latter were filled with cholesterol esters, and it appeared that we might be dealing with lipid accumulation of rather unique specificity.

By this time it was late September and it was getting cold on Chesapeake Bay, so without delay we sought a closer look at the geographical origin of these cholesterol-hungry cells. Dr. Altrocchi, would you take us briefly down to "the land of pleasant living"?

DR. PAUL H. ALTROCCHI: Although we might be somewhat biased, we feel that Tangier Island is an unusually interesting place for medical investigation. It represents one of those rare areas still extant in this country where geographical isolation has led to the development of a community in which a greater opportunity for manifestation of diseases determined by rare mutations is contrasted with a lack of evidence that such disorders are, indeed, occurring at an unusually high rate.

The island is located in the Virginia part of Chesapeake Bay, and its relatively simple mode of life is a refreshing change from that in more accessible regions. There is only one car on the island and no real streets on which to drive it. Practically all the males are fishermen, and the economy rises and falls with the fortunes of "the catch." Moreover, a diet high in fish and crab cakes, and the absence of a movie house, have not caused a general change in the islanders' tonsils. Dr. Fredrickson and I looked down the throats of at least one-tenth of the population without notable findings until, quite unprepared for the results, we examined E. L., the sister of our propositus, T. L.

In Figure 2 are shown the enormous

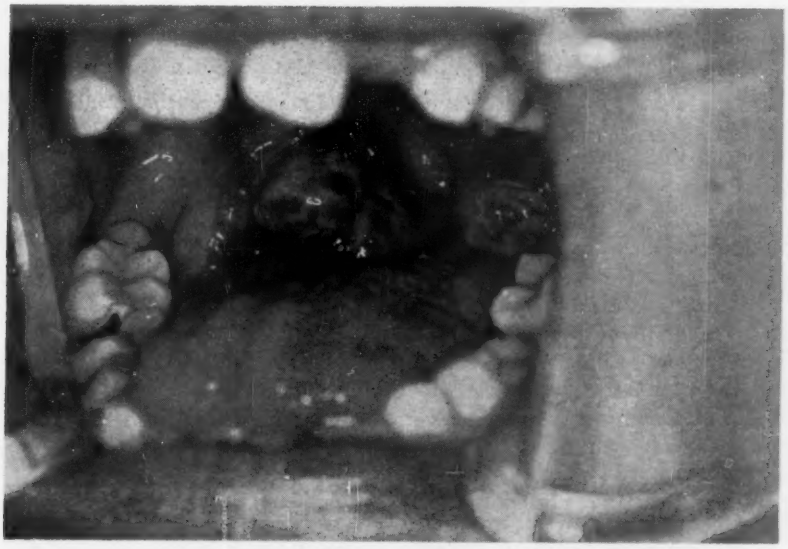

FIGURE 2. A view of the tonsils of E. L.

lobulated tonsils which greeted us when we looked in E. L.'s mouth. They fitted the description of her brother's in every way and were beginning to produce symptoms of obstruction. She was otherwise in excellent health, having neither hepatosplenomegaly, lymphadenopathy, nor neurological abnormalities.

We took steps immediately to admit E. L. to the National Institutes of Health for the purpose of tonsillectomy, a surgical procedure which, incidentally, is perhaps somewhat more difficult to arrange here than a craniotomy or open heart surgery. We also accepted referral of a Tangier Island fisherman who had recurrent tonsillitis and whose tonsils provided a "normal control" for analyses of E. L.'s tonsils.

The lipid content of these pairs of tonsils is shown in Table 1. Note that E. L.'s contain double the amount of the total lipid of the control. The esterified cholesterol fraction accounts for most of the difference, being 50 to 100 times the control. The free cholesterol is also twice the amount found in the normal control.

The several phospholipid classes separated by silicic acid chromatography (4) are also shown in Table 1. The tonsils of the control and of E. L. did not differ in their fractional phospholipid composition; hence, we were once again rather confident

TABLE 1. Tonsil Lipids in Tangier Disease

	mg per g wet wt Tissue	
	E. L.	H. M.*
Total lipid	32.3	17.7
Total cholesterol	14.5	2.3
Esterified	10.5	0.1
Free	4.0	2.1
Phospholipids	12.6	12.6
Cephalin	3.8	4.6
Lecithin	6.2	6.2
Sphingomyelin	1.9	1.6
Other	0.8	0.2
Cholesterol ester fatty acid	4.4	<0.1
Triglycerides	0.3	>0.1

* Control tonsils obtained from patient with benign tonsillar hypertrophy.

that in these children we were not dealing with a phospholipidosis such as Niemann-Pick disease but with abnormal storage of a neutral lipid.

DR. DONALD S. FREDRICKSON: So Tangier disease becomes a familial one and Niemann-Pick disease has been left far behind. Dr. Avioli, if one excludes the hyperlipidemic lipidoses such as essential hypercholesterolemia, about the oldest known disease in which cholesterol accumulates in tissues is the family of disorders including the Hand-Schüller-Christian syndrome. What can you say so far regarding the possibility that Tangier disease might actually represent one of these syndromes?

DR. LOUIS V. AVIOLI: Hand-Schüller-Christian syndrome is possibly better known as Hand-Schüller-Christian disease or eosinophilic xanthomatous granulomatosis. It is basically one form of a systemic disease which seems highly variable in its manifestations and includes granulomatous changes on the one hand, and probably Letterer-Siwe's disease, a more malignant histiocytic proliferative process, on the other. We can point out some differences between eosinophilic granulomatous disease and the pathological findings in these children.

As you remember, there were local accumulations of foam cells in tissues from T. L. In Hand-Schüller-Christian disease not only does one see these lipid storage cells, but there is also evidence of granuloma formation and reticuloendothelial or reticulohistiocytic hyperplasia. There may also be characteristic eosinophilic leukocytic infiltration. Of course, all these changes occur in various combinations dependent upon the stage of development of the lesion. The tissues of the L. children contained only foam cells. So, from a pathological point of view, it would be rather difficult to consider them consistent with eosinophilic xanthomatosis.

Thannhauser and Magendantz (5) and Cowie and Magee (6), for example, have reported some lipid analyses in lesions from Hand-Schüller-Christian disease. In addition to increased total lipids the total cholesterol ester fraction may be elevated. Of the phospholipids only separate lecithin determinations were reported; these were normal.

Perhaps there is chemical resemblance, but histologically the L. children's lesions do not fit into the category of Hand-Schüller-Christian disease.

DR. DONALD S. FREDRICKSON: Dr. Avioli, do you find such abnormal tonsils in Hand-Schüller-Christian disease?

DR. LOUIS V. AVIOLI: Some people have noted tonsillar hyperplasia but these tissues have never been analyzed for lipids.

DR. DONALD S. FREDRICKSON: Are any of these granulomatous diseases familial in occurrence?

DR. LOUIS V. AVIOLI: There are only two reported cases of so-called Letterer-Siwe disease which occurred in identical twins (7).

DR. DONALD S. FREDRICKSON: Confrontation by a storage disease which appears to be genetically determined naturally excites curiosity about alterations in enzyme activity which may be the root of the disorder. The search for the biochemical lesion initially demands close scrutiny of the material being stored for clues. With assistance of Dr. Arthur Karmen we took a closer look at the "cholesterol" esters in the L. tissues by gas-liquid chromatography.

It was first shown that essentially all the sterol in these lesions was cholesterol, and not some similar sterol. The fatty acid moieties of the cholesterol esters were also interesting, especially when compared to those in the plasma. In plasma cholesterol esters there is normally a preponderance of linoleic acid (8), and this was true in the L. children. Oleic acid predominated in the cholesterol esters obtained from both

the node from T. L. and the tonsils from E. L.

This difference in fatty acid pattern can be compared to another common type of cholesterol deposition. Dr. Evan Horning and his colleagues here have considerable unpublished data concerning cholesterol ester fatty acids in atheromatous plaques. In this instance they find an exaggeration of the plasma pattern, that is, even more linoleic than is usually seen in the plasma esters.

To examine further the specificity of this finding in the L. tissues, we determined cholesterol ester fatty acids in a bone marrow lesion from a case of Hand-Schüller-Christian disease supplied by Dr. Avioli. Here we found again a preponderance of oleic acid and very little linoleic acid. The pattern of ester fatty acids stored in Tangier disease therefore is not specific and does not offer a unique clue to the basic defect. We will mention these findings once again, however, because they adapt themselves to at least one theory about this disease.

Studies of cholesterol metabolism were next made in the two L. children. Before describing them, I would like to ask Dr. De Witt Goodman, of the National Heart Institute, to give us a brief summary of some important aspects of current understanding of cholesterol metabolism.

Dr. De Witt S. Goodman: The subject of cholesterol synthesis has been developing rapidly in the last few years. One of the most interesting aspects of this development has been the demonstration that this

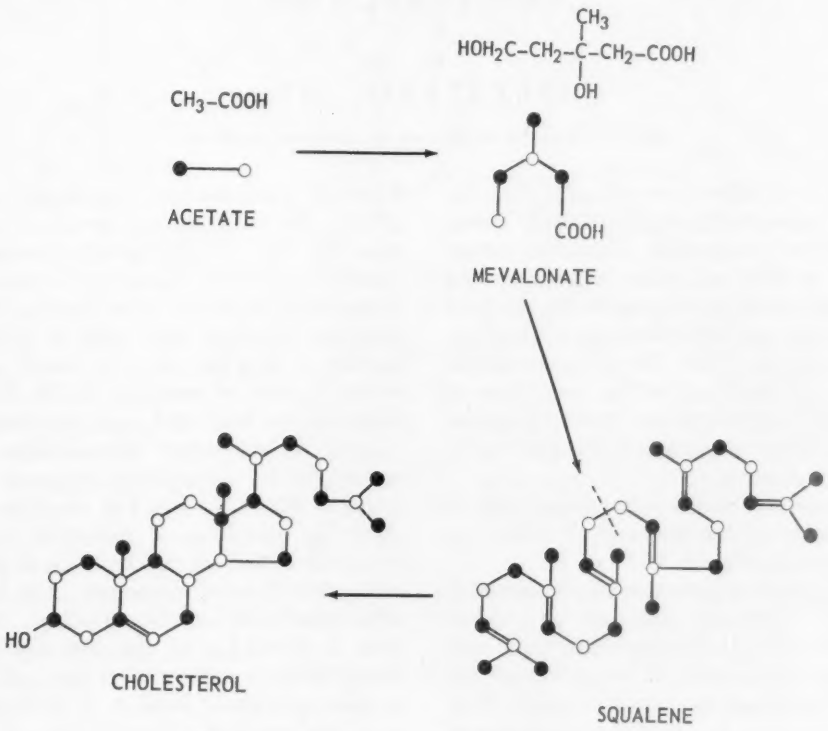

Figure 3. Important steps in conversion of acetate to cholesterol.

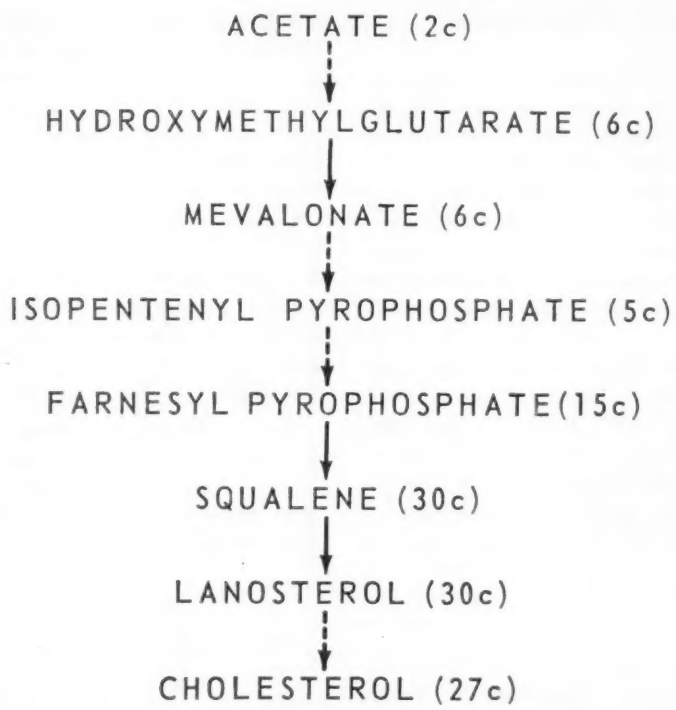

FIGURE 4. Sequence of reactions in cholesterol synthesis.

sterol, and, indeed, steroids as a class, belong biogenetically to a much larger family of diverse compounds including carotenoids, rubber and other terpenoids, and even the chemicals responsible for the scent of the rose and lily-of-the-valley. This family might be called the polyprenoids because it is built up by the association of units, each of which contributes a branched chain of five carbon atoms at the oxidation level of isoprene.

Let me summarize the present state of knowledge of the pathway of cholesterol biosynthesis (Figure 3).

The simplest precursor of cholesterol is acetate. Eighteen molecules of acetate traverse a long and complicated path, ending up as one molecule of cholesterol and nine molecules of carbon dioxide. This pathway starts by the joining together of three molecules of acetate to form the 6-carbon intermediate, mevalonic acid (MVA). Six molecules of mevalonic acid then lose their carboxyl groups, becoming 5-carbon isoprenoid units which join together to form the 30-carbon hydrocarbon, squalene. Squalene then folds or cyclizes directly to form the 30-carbon sterol, lanosterol. A series of reactions follow which elaborate the final cholesterol molecule.

Some of the other intermediates involved in this biosynthetic sequence are listed in Figure 4. The first reactions involve the activation of acetate to acetyl coenzyme A, and the condensation of three molecules of acetyl coenzyme A to form beta-hydroxyl-beta-methyl glutaryl coenzyme A (HMG Co A). Beta-hydroxyl-beta-methyl glutaryl coenzyme A is then reduced to form mevalonic acids. It is of interest that this reaction, the reduction of the former to the latter, appears to be one of

the most important loci of *in vivo* control of the rate of cholesterol synthesis.

The reactions following the formation of mevalonic acid involve a series of phosphorylations in which MVA reacts serially with three molecules of adenosine triphosphate and loses its carboxyl group as carbon dioxide to form the 5-carbon intermediate, isopentenyl pyrophosphate. This compound is the long-sought-for "active" isoprenoid, the condensation of six units of which forms squalene. As indicated in Figure 4, there occurs first a condensation of three molecules of isopentenyl pyrophosphate to form the 15-carbon intermediate, farnesyl pyrophosphate, two molecules of which join together, with elimination of their pyrophosphate groups, to form squalene.

When squalene cyclizes to sterol, the first product formed is lanosterol. The series of reactions which this molecule undergoes are summarized in Figure 5, and include, first, the loss of the three extra methyl groups in positions 4, 4′, and 14; then, the shift of the nuclear double bond from position 8, 9 to 5, 6; and, finally, the reduction of the extra double bond at 24, 25.

The final intermediate in this sequence is very likely 24-dehydro-cholesterol, or desmosterol. This sterol has been a focus of much recent interest because of the demonstration that the hypocholesterolemic drug, triparanol (MER/29), blocks the conversion of desmosterol to cholesterol. This results in the accumulation of desmosterol in the serum and tissues of animals and patients treated with this compound. This finding, I should add, does not absolutely

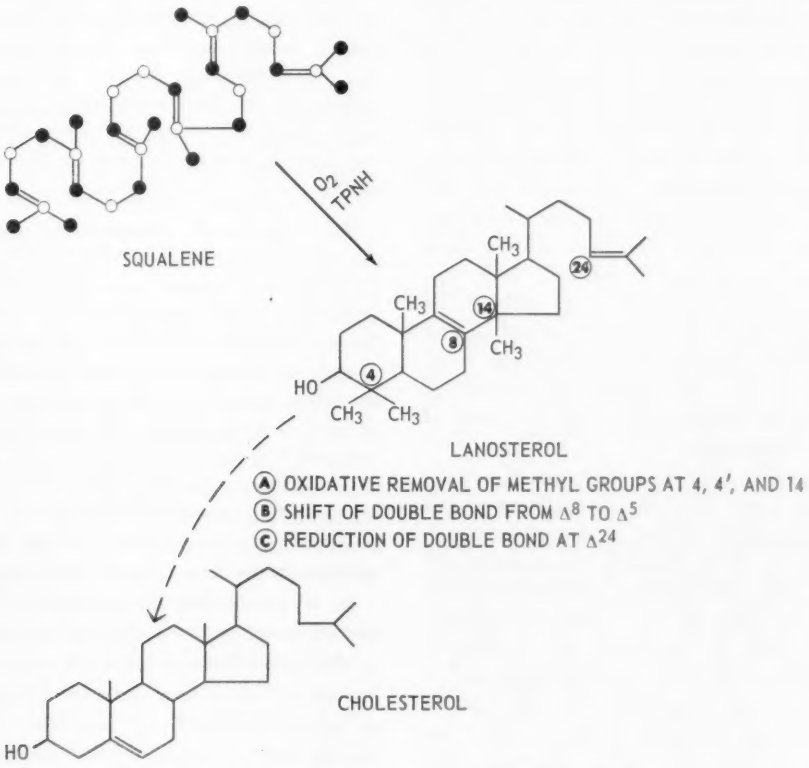

FIGURE 5. Conversion of lanosterol to cholesterol.

prove that desmosterol is normally the final intermediate in cholesterol synthesis, and we are currently engaged in studies to try to decide this question.

Let me conclude with a brief look at the subject of cholesterol ester metabolism since it seems closely related to the disease under discussion.

Let us consider first the intestinal lumen. Here dietary cholesterol is diluted by endogenous sterol, which comes from the bile and also from the intestinal wall. The intestinal wall, I should add, is a place where considerable *de novo* synthesis of cholesterol from acetate takes place and where a sterol pool of considerable size exists. The sterol in the gut is largely unesterified, any esters having been hydrolyzed by pancreatic esterase.

During absorption of cholesterol from the intestinal lumen into the lymph, about 75% of the sterol becomes esterified. Thus it is obvious that the intestinal wall is also a major site of cholesterol esterifying enzyme activity. The details of this esterification are still uncertain. Much is known about the pancreatic cholesterol esterase, which has been studied in great detail and purified more than 400 times. This enzyme appears to catalyze both hydrolysis and formation of cholesterol esters without the involvement of any necessary cofactors; and it has been claimed that this enzyme is responsible for the cholesterol esterifying activity of the intestinal wall, but proof of this is incomplete.

The other major site of cholesterol esterification is the liver. Here, too, most of the sterol is present in free form; and here, too, the details of cholesterol esterification are very poorly known. There is some evidence that coenzyme A and adenosine triphosphate may be necessary for cholesterol esterification by liver homogenates, and it has thus been suggested that this process involves the formation of a fatty acyl coenzyme A derivative before reaction with cholesterol to give cholesterol ester. This is, *a priori*, a very reasonable scheme, but the evidence is still quite incomplete, and more details would be desirable.

When we consider plasma cholesterol esters, the form in which 75% of plasma sterol is present, the gaps in our knowledge become even more obvious. There is a lively controversy, for example, over the source of these esters, one group maintaining that the intestine is the major source and others holding that they come exclusively from the liver. One way to resolve this question might be through analysis of cholesterol ester fatty acids, comparing those in plasma with those in intestinal lymph and liver. As Dr. Fredrickson has already indicated, the plasma cholesterol esters contain a high percentage of essential, or polyunsaturated, fatty acids, linoleic being the predominant acid in man. In the rat, arachidonic acid, with four double bonds, is often the predominant acid. Unfortunately neither the intestinal lymph nor the liver sterol ester fatty acids have the same composition so that this question cannot be decided by this simple means.

DR. DONALD S. FREDRICKSON: Immediately after their removal, tonsil slices from E. L. and the control were incubated with both acetate-C^{14} and mevalonic acid-C^{14}. There was brisk synthesis of cholesterol from both precursors in both sets of tissue, the slices from E. L. being perhaps twice as active. It is impossible to determine, however, from this single experiment whether the suggested greater rate of sterol synthesis in the abnormal tonsils could account for the enormous storage of cholesterol in the reticuloendothelial tissues.

It is interesting that mevalonic acid proved to be no more efficient than acetate in the tonsil slices, as opposed to its much greater efficiency as a cholesterol precursor in other systems (9). It was also demonstrated that a considerable amount of mevalonic acid radioactivity (20%) was still

present in squalene after four hours' incubation.

A small amount of labeled mevalonic acid was also given intravenously to the two L. children, and the resultant radioactivity in plasma free and esterified cholesterol was followed. As far as we can compare the results to those of normal adults given labeled mevalonic acid, the rates of esterification and turnover of endogenously synthesized cholesterol in the plasma appeared to be normal.

Dr. Goodman, do you have any comments before we go on?

DR. DE WITT S. GOODMAN: Only that from your description tonsils seem to make cholesterol quite adequately, and I have no explanation for the large fraction of labeled squalene remaining.

DR. DONALD S. FREDRICKSON: The tonsil slice experiments demonstrated considerable metabolic activity of this tissue, and we are employing it for study of metabolism of other lipids. They are an unusually accessible source of reticuloendothelial tissue for this purpose.

Despite those studies described, we still did not have our hands on the responsible lesion in the L. cases. In most other known tissue lipidoses the plasma lipids are either normal or not specifically altered and do not seem to offer a clue to the basic mechanism involved. Perhaps for this reason the routine lipid analyses on the two L. children were left unattended in the record book until after our patients had returned home. When these analyses were studied, the simplest clinical guide to this disease proved in retrospect to have been available from the beginning.

In Table 2 are shown the plasma lipids in E. L. She is compared here and in subsequent figures to two normal children of the same age. There are two significant clues. One, the cholesterol in E. L. of 85 mg/100 ml, is much too low for our American population, even at her age of six.

TABLE 2. Plasma Lipids in Tangier Disease

	E. L.	Normal*
Total lipid	444	512
Total cholesterol	85	170
Free cholesterol	23	46
Total phospholipid	82	231
"Triglyceride"	237	40

* Mean of separate determinations of plasma from normal male, age 6, and female, age 8.

Secondly, the triglyceride concentration is also too high for normal postabsorptive plasma. This latter means that some of the triglyceride-bearing low density lipoproteins must be elevated in concentration, but this cannot explain the paradoxically low total cholesterol value. Thus, it became necessary to determine separately concentrations of the several lipoprotein classes.

There are several methods available for quantifying the lipoproteins in the plasma, probably the most widely used being electrophoresis and ultracentrifugation. Extensive studies in recent years have demonstrated that there are two major species of soluble lipoproteins differing quantitatively in lipid content and qualitatively in their protein portions (10). These are known as high density lipoproteins when the ultracentrifuge is used for separation, or alpha-1 lipoproteins when electrophoresis is used, and low density lipoproteins or beta lipoproteins when separation is by paper electrophoresis. Some of the low density lipoproteins may also migrate as alpha-2 lipoproteins on starch.

As mentioned, the protein portions of the low and high density lipoproteins are specific and differ in structure, antigenicity, and metabolic behavior. For example, the proteins, as opposed to the lipid moieties, do not interchange when tagged lipoproteins of the two major classes are mixed (11). Presumably, these proteins have different functions as well as origins, but very little is known about either aspect of these interesting lipid-avid molecules.

TABLE 3. Lipoprotein Cholesterol

Density		E. L.	Normal*
<1.019	(LDL)†	43	12
1.019–1.063	(LDL)	29	65
1.063–1.21	(HDL)‡	2	56

* Mean of separate controls (see Table 2) fractionated concurrently.
† LDL = low density lipoprotein.
‡ HDL = high density lipoprotein.

When fat is being absorbed from the gut, another form of "lipoprotein," chylomicrons, appears in the lymph and then plasma. These are large (0.5 to 1 micron) particles of triglyceride, also containing small amounts of cholesterol esters, phospholipids, and protein. Studies by Dr. Rodbell and ourselves (12) and by Scanu and Page (13) have demonstrated that some of this protein appears to be similar to or identical with the alpha or high density lipoprotein. Whether this latter results from fortuitous contamination or more meaningful biological design is not yet known.

With this brief orientation let us look at the ultracentrifugal analyses of plasma lipoproteins in E. L. (Table 3). The method of Havel, Eder, and Bragdon (14) was used, and cholesterol is shown here as the index to lipoprotein concentration. Note that there is some increase in low density lipoproteins, but the striking feature is the almost complete absence of cholesterol between the densities where the high density lipoprotein fraction should have been recovered. The same was true for phospholipids, both lipids being present normally in these lipoproteins.

Failing to find the high density lipoproteins by flotation, we next sought information concerning the protein portion of this lipoprotein by analyses not dependent upon lipid determinations. For this purpose immunochemical techniques offer sensitive and reliable assay. In this we are greatly aided by Dr. Howard C. Goodman of the National Institute of Allergy and Infectious Diseases.

DR. HOWARD C. GOODMAN: Two characteristics of lipoproteins, their electrophoretic mobility and their antigenic properties, are useful in identifying and measuring them at least semiquantitatively. In a simple electrophoretic separation in gel followed by staining with Sudan black, only a single band with slow mobility, corresponding to the low density or beta lipoprotein, was obtained with the serum from E. L.

In order to add immunological characterization in the technique named immunoelectrophoresis, after the proteins have been separated by electrophoresis, a trench can be cut in the gel parallel to the separated proteins and filled with an antiserum prepared against normal human serum. Antigen-antibody precipitation lines are then formed. Those containing lipids can then be selectively stained and the lipoproteins more specifically identified. When this was done, only the low density beta lipoprotein precipitation line was obtained with E. L.'s serum, contrasted to the two distinct lipoprotein lines obtained with normal serum. When all of the precipitation lines were colored by a protein stain, all the other precipitation lines characteristic of proteins in normal serum from gamma globulin to albumin appeared in E. L. as they did in the normal serum. In a variation of the same technique, an antiserum reacting primarily with the high density human alpha lipoprotein was used; and again the alpha line was missing in the E. L. serum.

This is a bit more complicated than is required for screening tests, and Figure 6 shows the more straightforward Ouchterlony technique which requires only a Petri dish containing a layer of agar gel, in which a pattern of holes is punched. Human serum was placed in the central holes, and in the surrounding six holes rabbit

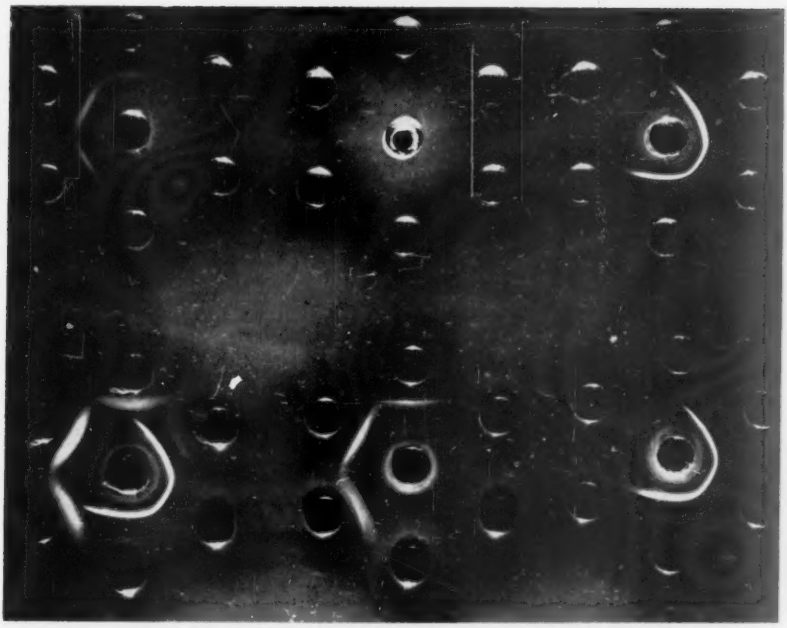

FIGURE 6. Qualitative determination of plasma lipoproteins by precipitation lines formed from antigen-antibody reaction using the agar diffusion technique. In each group the center contains human serum; the two holes at the left and the top, rabbit antibody to human high density lipoprotein; and the bottom and two holes to the right, rabbit antibody to human low density lipoprotein. At the lower left precipitation lines for both lipoproteins are obtained with normal serum; the lower middle shows the absence of low density lipoprotein in serum from a patient with a-beta-lipoproteinemia; at the lower and upper right is seen the almost complete absence of any precipitation line for high density lipoproteins in sera from E. L. and T. L. The other reactions shown are not pertinent.

antisera to the two different human lipoprotein classes. After the antisera and the patients' sera had been allowed to diffuse together for about 24 hours, immune precipitates formed. You will note that lines corresponding to both alpha and beta lipoprotein have formed in the normal. A second serum from a patient with a-beta-lipoproteinemia and acanthocytosis has no beta lipoprotein line. The sera from E. L. and her brother, T. L., form good lines with the antisera to beta lipoproteins, but only very faint lines with antisera to the high density or alpha lipoproteins. By doing this test with several dilutions of normal serum, it was determined that the normal serum contained at least 60 to 100-fold greater amounts of alpha lipoprotein than sera of the L. children.

Thus, these data confirm the ultracentrifugal findings and indicate complete or almost complete absence of serum alpha lipoprotein in these two patients. I am very curious, after hearing the early part of the presentation, to know whether any of the Hand-Schüller-Christian sera had been so tested.

DR. DONALD S. FREDRICKSON: I am glad you asked that last question, Dr. Goodman. We, too, have been curious about it and have stored such sera for your future examination.

The illustration just shown (Figure 6) is particularly noteworthy since it gives us an opportunity to present side by side for the first time what may be two genetically determined diseases manifesting as de-

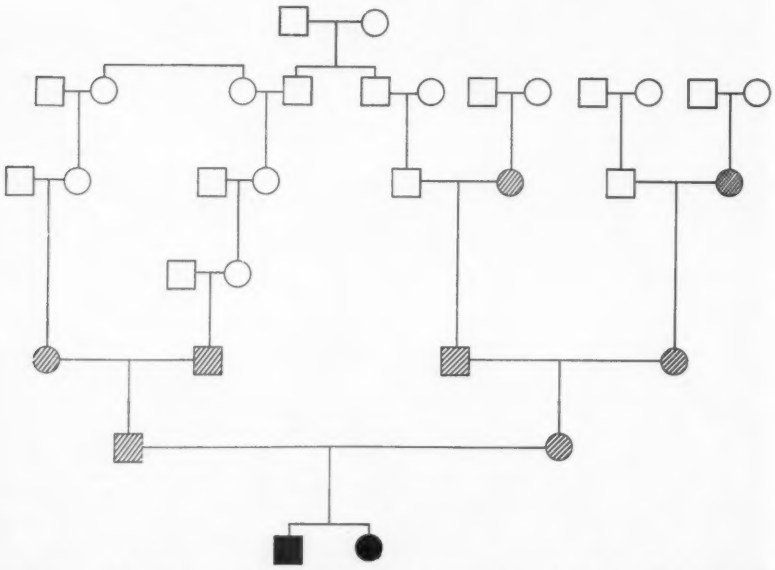

FIGURE 7. A partial pedigree of the L. children. The propositi are shown in solid symbols. The crosshatched symbols indicate relatives examined, none of whom had tonsillar hypertrophy.

ficiency of different lipoproteins. The patient with a-beta-lipoproteinemia, currently being studied here by Dr. Leonard Laster, is one of a very small group which has, in addition to absence of the lipoprotein, acanthocytosis, ataxic neuropathy, retinopathy, and malabsorption of fats. The interrelationship of these abnormalities is not understood, but it has been suggested that they may include a genetically determined inability to make beta lipoprotein (15). It is also interesting to note how different are the clinical abnormalities associated with deficiency of one of these two different lipoprotein classes.

We have also determined the plasma lipoproteins of the mother, P. L., on a single occasion. The concentration of her high density lipoproteins was also low, about half of the average published values for her age and sex (14).

These abnormal values will require confirmation, but if the mother proves to be an example of a "carrier" state detectable by lipoprotein analyses, this is a rather fortunate mendelian set of affairs from the standpoint of further study of this disease. She and her husband appear to be perfectly healthy. Both E. L. and her mother do have a moderate number of large foam cells in bone marrow aspirations viewed in supravital preparations. However, unlike those seen in Niemann-Pick disease, for example, these cells do not survive alcohol fixation and staining.

Dr. Altrocchi will now give us some background information about Tangier Island and the L. pedigree.

DR. PAUL H. ALTROCCHI: Tangier Island was discovered in 1608 by Captain John Smith, who only one year previously had founded Jamestown. After its discovery the Island was without a single lipidosis, in fact without a single inhabitant for the next 78 years when in 1686 one John Crockett founded a settlement there. Today a large percentage of the approximately 900 people on the Island are apparently descendants of the original settler and bear his surname.

A partial pedigree for the L. children is shown in Figure 7. The crosshatched areas represent patients whom we examined and who had neither abnormal tonsils nor lymphadenopathy. Their lipoproteins have not yet been measured. The parents of the L. children are at least distantly related and the pedigree could be consistent with the full-blown syndrome's being an expression of homozygosity for an autosomal recessive trait. The pedigree is much more complex than is demonstrated here, and genetic studies of this interesting family have just begun.

DR. DONALD S. FREDRICKSON: Thus, we have two young siblings with tonsils of extraordinary size and appearance, enlargement of the liver, spleen, and lymph nodes, and hypocholesterolemia. These findings are related to the presence of reticuloendothelial cells laden with very large amounts of cholesterol esters and the complete, or almost complete, absence of plasma alpha or high density lipoproteins. To my knowledge such deficiency of high density lipoproteins has never been reported. The specific accumulation of cholesterol esters in tissues is also unusual, for several different lipid classes tend to be elevated in most other instances of tissue lipid storage. Hence, we are apparently dealing with a new disease; and the available data suggest it is a genetically determined one. Until the disease can be described in terms of the basic defect, we have chosen to call it simply "Tangier disease."

The nature of the inheritable primary defect remains speculative. Let us assume the primary "biochemical lesion" to be inability to make the normal protein complement of the high density lipoprotein molecule. If this be so, then the absence of this lipoprotein in plasma causes histiocytic cells in many tissues to store outrageous amounts of cholesterol esters. What normal pathway could be disturbed to produce this chain of events? Tissues other than liver have been considered to account for little or none of the normal amount of endogenous cholesterol in plasma (16). There is also low density lipoprotein available for cholesterol transport, and the amounts are increased in these patients. Furthermore, absence of low density lipoproteins, as mentioned above, is not known to produce such tissue lipid storage. Perhaps, then, high density lipoprotein does have some specific and yet unrecognized role in endogenous lipid transport and possibly one closely related to sterol esterification. The reticuloendothelial cells here may be directly involved or else are exercising secondarily their well-known capacity for scavenging unwanted lipid.

The absence of high density lipoprotein might also result in a defect in the transport of exogenous lipid. The presence of these lipoproteins in chylomicrons could imply a role in the normal metabolism of these large fat particles. Although chylomicrons contain mainly triglyceride, the cholesterol esters arising in the intestine are also carried in this manner. As you recall, we were first intrigued by the fatty acid pattern in the stored cholesterol esters, the predominance of oleyl residues being more in keeping with the fatty acid in newly absorbed cholesterol esters than in those present postabsorptively in plasma. Should chylomicrons be rendered less stable by absence of the high density lipoprotein, their lipids might be removed preferentially by reticuloendothelial tissues. The later finding that cholesterol esters deposited in tissues in other diseases also have a similar fatty acid pattern makes this explanation less likely. The ability of the L. children to absorb fat and to elaborate chylomicrons will be studied next to clarify the essentiality of high density lipoproteins in these processes.

There are many possible alternative mechanisms, of course. There is the theo-

retical possibility that these patients manufacture alpha lipoproteins but that the reticuloendothelial cells immediately remove them from circulation and retain their sterol portion. This hypothesis might be made plausible if it also assumed that the lipoprotein molecules were abnormal in structure and, hence, more susceptible to removal. The single study of tissue synthesis of cholesterol unfortunately proves only that the tissues could manufacture their stored lipids *in situ*, not that they necessarily do so.

Obviously, we know too little of the normal functions of the specific lipoproteins to answer the many questions that have arisen. One of the remarkable opportunities that patients with rare genetically determined diseases offer is an occasional view of normal processes obtainable in no other way. Possibly Tangier disease will provide us with just such a view into some now-clouded aspects of fat transport and metabolism.

Acknowledgment

The cooperation of Drs. J. Thomas Edmonds, of Accomac, Virginia, and Issac White, of Bloxom, Virginia, in arranging for studies of these patients is gratefully acknowledged.

Summario in Interlingua

Es discutite le caso de duo juvene fraternos con tonsillas de magnitude e apparentia extraordinari, con allargamento del hepate, del splen, e del nodos lymphatic, e con hypocholesterolemia. Iste constatationes es relationate con le presentia de cellulas reticuloendothelial, cargate con grandissime quantitates de esteres de cholesterol e le absentia complete —o quasi complete—de lipoproteinas alpha o lipoproteinas de alte densitate in le plasma. Un tal carentia de lipoproteinas de alte densitate ha nunquam essite reportate. Le accumulation specific de esteres de cholesterol in certe tissus es etiam inusual, proque plure differente classes de lipido tende a esser elevate in le majoritate del altere exemplos de magasinage tissular de lipido. Il se tracta hic apparentemente de un nove morbo que es geneticamente determinate. Usque le morbo pote esser describite a base de su defecto fundamental, illo ha essite designate "morbo del Insula de Tangier" secundo le sito de su origine. Le detection del morbo es discutite con referentias al metabolismo de lipido e al lipidoses.

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WHEN DOCTORS ARE PATIENTS

THE PHYSICIAN who has himself been sick is alert to detect the fluctuations in the well-being of the patient which accompany changes in physical state and mood, each of which is reflected in the other. Such a physician is endowed also with the rare quality better described as understanding than as sympathy. It is, after all, for understanding rather than pity that the average patient seeks a doctor, yet this important talent is far harder to acquire than the facile half-virtue of sympathy; both the praise and scorn of the public for the latter are well summarized in the phrase "bedside manner." This sensitivity is augmented when one is oneself most ill; although the sick physician is never guilty of the coldness which sometimes blemishes his healthy colleague, his own understanding of patients is greatly enhanced when he is himself most in need of understanding. Under these circumstances a sort of grace may illume the physician in his work.

The sick physician becomes aware also of the avidity with which a patient will clutch and possess every word uttered by the doctor. So great is the ignorance of the layman in medical matters that his doctor's statements have for him an oracular significance which the physician rarely appreciates—until he has himself been dejected by a gesture or encouraged by a smile.—IAN STEVENSON: Observations on illness from the inside (bronchiectasis), in *When Doctors Are Patients,* ed. by Pinner, M., and Miller, B. F., W. W. Norton and Company, Inc., New York, 1952, Ch. 21.

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EDITORIALS

Amyloidosis: Tissue Proteinosis: Gammaloidosis

THE THREE ARTICLES dealing with "amyloidosis" which appear in this issue of the ANNALS are testimony to the continuing interest in this vexingly obscure clinical and experimental phenomenon. Despite the extensive studies of the subject which have been carried out over the past several decades, the precise pathogenesis and exact biochemical nature of these infiltrates are still incompletely understood. Some progress has been made, however, and it may be in order to summarize briefly our present knowledge and some of the current "working hypotheses."

At the outset, it may be appropriate to examine and possibly to challenge the validity of the term "amyloid" itself, in the light of the conclusive evidence that these infiltrates are more proteinaceous, albeit glyco-proteinaceous, than "starch-like." As originally emphasized by Apitz (1) in 1940, the consistent demonstration of a protein moiety in both the "primary" and "secondary" infiltrates would seem to outweigh their inconsistent tinctorial behavior, *i.e.,* iodine staining, which was the basis for Virchow's designation. Apitz suggested the term "tissue proteinosis" as being more precise than "amyloid," but despite the accumulation of biochemical justification for Apitz' term, it has not succeeded in replacing "amyloid" and its many modifiers ("para-," "systematized," "primary," "secondary," etc.) in general usage. In some measure this may be due to the fact that *both* protein *and* carbohydrate moieties have been shown to be present in these infiltrates, but the resemblance of the substance to starch *per se* would seem to be superficial, indeed.

Although the precise chemical composition of these glycoprotein infiltrates remains to be determined, an increasing body of evidence indicates their relationship to the immunoglobulins, *i.e.,* to the gamma globulins as broadly defined by Heremans, Waldenström, Grabar, and others. Specifically, the histochemical studies of Teilum (2) have demonstrated that the "secondary" and experimental amyloid * infiltrates which develop after prolonged and excessive antigenic stimulation are formed *in situ* by cells of the reticuloendothelial system, cells that have proliferated and differentiated along "plasmocytic" lines in a manner essentially similar to the normal cellular response to antigenic stimulation. The pathological process of "amyloid" formation, however, differs from the normal process of immunoglobulin production in that the glycoprotein product(s) of the abnormally-stimulated reticuloendothelial cells are not carried away into the general circulation, but rather remain in juxtaposition to these cells in the form of insoluble aggregates. The fact that the glycoproteins of "amyloid" are *different* from the normal gamma immunoglobulins is implicit in this difference in solubility; but certainly of equal significance is the evidence which demonstrates the major *similarities* between "amyloid" and gamma globulin. These similarities have been most conclusively shown by the immunohisto-

* The presently available evidence indicates the experimentally induced forms of amyloidosis and the "secondary" amyloidosis which develops in association with various chronic disease states *other than plasma cell myeloma* are essentially similar, if not identical processes, and will be considered together in this discussion.

chemical studies of Vasquez and Dixon (3) with the demonstration of highly specific staining of "secondary–experimental amyloid" deposits with fluorescein-labeled anti-normal gamma globulin. Thus, it has been established that this form of "amyloid" contains certain of the structural and chemical, *i.e.*, antigenic determinants present in the normal gamma immunoglobulins and is, in fact, formed by the same family of cells. These data have seemed of sufficient importance to the present author to suggest that the designation "gammaloid," may be more correct and possibly more meaningful than "amyloid," and with the reader's permission, this will be the term employed in the remainder of this article.

Considering further the evidence that "gammaloid" shares several features in common with the immunoglobulins, *i.e.*, source of production, conjugated carbohydrate, and antigenic determinants, there still remains the most important question as to the precise composition of these insoluble aggregates. A few of the several possibilities which have been suggested by different investigators can only be mentioned in the hope that they may be provocative of further consideration and investigation; *viz.*, antigen-antibody complexes; aggregates (polymers) of normal or pathological 7S or 19S immunoglobulins; complexes of normal or pathological immunoglobulins with other serum or tissue protein or polysaccharide constituents. Of possible pertinence to these considerations is the increasing body of evidence which indicates a propensity of both normal and pathological immunoglobulins to form protein: protein and protein: polysaccharide complexes, as exemplified by several of the rheumatoid serological reactions. Indeed, in a study of tissues from a patient with rheumatoid arthritis who died with "secondary gammaloidosis," † Mellors and coworkers (4) have conclusively demonstrated by the Coon's technique the presence of both 7S gamma globulin and 19S macroglobulin in the renal and splenic infiltrates.

At the present time, it may be presumed that the "gammaloid" infiltrates which develop in the organs and tissues (*e.g.*, the liver, spleen, and lymph nodes) which normally contain large numbers of cells of the so-called reticuloendothelial system are actually formed by these cells, and there is ample evidence to support this premise. The formation of "gammaloid" in other "non-reticuloendothelial" sites, particularly those in which mononuclear cell infiltrations are not observed, however, would seem to require another explanation. These latter sites, principally the perivascular regions of small arterioles, in the glomerular capillaries, surrounding cardiac, nonstriated and occasionally striated muscle cells, in the perineural sheaths, etc., are the regions *characteristically* involved in the so-called "primary" form of the disease and in association with overt plasma cell myeloma, but they are also not infrequently involved to a greater or lesser extent in the "secondary-experimental" form. To explain this occurrence, it has been suggested that multipotential reticuloendothelial cells of these regions may differentiate into immunoglobulin-forming cells under the stress of prolonged stimulation or hyperimmunization. This postulate, however, would seem unlikely in view of the failure to demonstrate in these regions the cytochemical features which are almost universally associated with protein synthesis, particularly an increased content of ribonucleoprotein, as indicated by pyroninophilia or an abundance of endoplasmic reticulum as shown by electron micrography. As an alternative hypothesis, it may be suggested that one or more of the constituents of these pathological infiltrates is a soluble component which is carried to the site of deposition by the circulation, and that the insoluble infiltrate represents a complex between a specific cellular protein or polysaccharide and this circulating constituent.

† Paraphrased with the permission of Dr. Robert Mellors.

The immunohistochemical studies previously mentioned would indicate that the circulating constituent is most commonly an immunoglobulin or, possibly, an immunoglobulin fragment.

Up to this point, we have been principally concerned with the "secondary-experimental" form of "gammaloid." We shall now turn our attention to the so-called "primary" variant and that which is associated with plasma cell myeloma. As noted in the article by Briggs (5) in this issue, there has developed increasing evidence in recent years (6, 7) which supports the thesis of Apitz (1) and Magnus-Levy (8) that many, if not all, of the "primary" cases are actually cases of occult plasma cell myeloma, *i.e.,* individuals with a plasmocytic dyscrasia which is diffusely distributed throughout the skeletal system and not accompanied by clinically-evident skeletal destruction. As demonstrated by Apitz (1), the abnormal plasma cell infiltrates can be demonstrated in these "primary" cases if multiple bone marrow sections are examined in detail, and, indeed, if a patient with "primary amyloidosis" survives for a sufficient number of years, overt skeletal destruction may eventually develop. The possibility that *all* cases of "primary amyloidosis" represent examples of occult plasma cell myeloma seems unlikely at present, but unquestionably the association exists in a much higher proportion of cases than previously suspected (6, 7).

What is the evidence that the "primary-myeloma" infiltrates may also be "gammaloid"? Apitz (1) and Magnus-Levy (8) were the first to suggest that these tissue infiltrates might represent another type of protein metabolic derangement akin to the Bence Jones proteinuria and hyperglobulinemia of myeloma. Indeed, Magnus-Levy (8) further speculated that Bence Jones proteins might be *etiologically* related to the tissue infiltrates because of the observed high frequency of Bence Jones proteinuria in cases of overt or occult myeloma with associated "tissue proteinosis." As previously reported from this laboratory (6), this high order of association has been confirmed and extended through the application of the more sensitive analytical techniques of electrophoresis and immunoelectrophoresis. To date, in 18 of 19 patients with "primary tissue proteinosis" and overt or occult myeloma, Bence Jones proteinuria, characteristic myeloma serum globulins, or both have been demonstrated, with the great majority (16 of 18) exhibiting Bence Jones proteinuria. A wealth of physicochemical and immunochemical data has established that these myeloma "paraproteins" are very closely related to the 7S gamma immunoglobulins (γ2 and γ1A). Although each myeloma serum globulin and each Bence Jones protein would appear to be individually specific, they all have been shown to contain antigenic determinants, *i.e.,* structural groupings, in common with the 7S immunoglobulins. Accordingly, all of the myeloma serum and urinary proteins cross react with antiserum to 7S gamma globulin. Thus, the demonstration in this laboratory (9) of staining of "primary-myeloma amyloid" by both an anti-Bence Jones antiserum and an antiserum to normal 7S gamma globulin labeled with fluorescein could only be interpreted as confirmatory of the "gammaloid" nature of the material, but not as proof of a specific role of certain of the low molecular weight (MW 35–40,000) Bence Jones constituents, as postulated in reference (6). More recent studies (9), however, in which individual Bence Jones proteins have been labeled, and their specific tissue binding affinities examined, have provided considerably greater support for this hypothesis. Whether certain of the 7S myeloma serum proteins with molecular weights in the range of 160,000, or even 19S macroglobulins can also be involved in the pathogenesis of these infiltrates in some of these cases remains to be determined.

Although one is reluctant to propose a new nomenclature system for the "tissue

proteinoses," the weight of evidence which indicates a major role of the gamma immunoglobulins in the pathogenesis of the "primary-myeloma type," and the "secondary" and experimental forms would seem to validate the substitution of the "gamma" root in the designation of these specific infiltrates. It should be stressed, however, that it would be entirely incorrect to apply the term "gammaloid" to those conditions, particularly the familial form, and the form associated with familial Mediterranean fever, in which immunohistochemical studies have not, as yet, been reported. The possibility that plasma proteins other than the immunoglobulins (particularly fibrinogen and the alpha glycoproteins) may be constituents of tissue infiltrates in certain disease states remains to be determined.

ELLIOTT F. OSSERMAN, M.D.
Department of Medicine
Columbia University College of
Physicians and Surgeons and
Francis Delafield Hospital
New York 32, New York

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Drug Therapy and the Etiology of Systemic Lupus Erythematosus

ALTHOUGH many theories concerning the cause of lupus erythematosus (SLE) have been advanced, the precise etiology of this disorder remains obscure. Most investigators now believe that the symptomatology and ultimate pathology in this condition are attendant upon an abnormal hypersensitivity state. Evidence for this concept is the occurrence of antibody activity in a variety of plasma proteins to various cell types of the human body during the course of the disease (1). Although these antibodies vary from patient to patient, their appearance and disappearance are related to the activity and inactivity, respectively, of the disease process (2).

Reports of the apparent production of systemic lupus erythematosus by an ever-increasing number of commonly used drugs have appeared in the literature within the past decade. The original observation that the long-term use of hydralazine (3–7) in certain patients was eventually accompanied by a multisystem disease very similar to systemic lupus erythematosus, with or without renal involvement, was followed by reports of similar occurrences in patients receiving penicillin (8, 9), phenylbutazone (10), sulfadiazine (11, 12), methylphenylhydantoin (13) trimethadione (14, 15), and sulfamethoxypyridazine (16).

The increasing number of drugs that

produce this reaction or one similar to it compel one to consider, more seriously than was done in the past, the role of extrinsic factors in its etiology. To be precise about extrinsic factors in the etiology of systemic lupus erythematosus is difficult since, unfortunately, the natural history of the disease in man is not known. Arbitrarily, the onset of the disease in a given patient is historically antedated to that time when even a set of feeble symptoms suggested the diagnosis. Indeed, the purists concerned with this riddle date the onset of the disease from the time of definitive laboratory proof of the disorder. Enhanced clinical and diagnostic acumen and awareness of the disease permit earlier diagnosis today. Even so, the natural history of the disease remains uncertain and therefore the determination of other extrinsic factors that are of importance is most difficult.

The hydralazine syndrome, which has been extensively studied, progresses from mild arthralgia to a clinical state compatible with rheumatoid arthritis. If administration of the drug is continued classical symptoms of systemic lupus erythematosus supervene. That hydralazine plays a causative role in producing this syndrome is substantiated by the following facts: [1] The symptoms and signs of the reaction usually regress rapidly upon withdrawal of the drug, the arthritis often disappearing within 24 hours thereafter. [2] Subsequent administration of the drug, even in very small doses, causes a prompt recurrence of symptoms in most, but not all, instances, the symptoms being more severe than during the original reaction (4).

Is the "hydralazine syndrome" in reality idiopathic systemic lupus erythematosus, or is it a separate syndrome that is clinically indistinguishable from the idiopathic form? Using the present criteria for diagnosis, patients with the "hydralazine syndrome" fulfill all of the requisites for the diagnosis of systemic lupus erythematosus. The recent demonstration by electron microscopy of the histologic renal lesions typical of this disease in patients with the like syndrome after trimethadione therapy is strong evidence that the reactions developing subsequent to drug administration and idiopathic systemic lupus erythematosus are one and the same disease (15).

The development of a similar syndrome in conjunction with drug therapy has aroused considerable speculation on the pathogenesis of idiopathic systemic lupus erythematosus. Could the development of the drug-induced syndrome be explained on the basis that such a reaction occurs only in patients with the latent form, that is, an "unmasking" of latent disease (17)? This concept does not seem plausible since one would be forced to postulate that 10% of all of the patients with arterial hypertension being treated with hydralazine and developing the drug-induced syndrome have latent systemic lupus erythematosus (18).

Because of the multiplicity and sequential variation of symptoms of the idiopathic disease, the diagnosis is often long delayed. By the same token it is possible that the occurrence of similar drug reaction in a mild form may remain long unrecognized clinically. Therefore, the actual incidence of such drug reactions may be far greater than previously supposed. In addition, the development of a more severe form of the disease may have been prevented by withdrawal of the drug at the onset of symptoms of drug intolerance. The occurrence of spontaneous remissions in one-fourth to one-third of patients with idiopathic systemic lupus erythematosus who have received no therapy for the disorder suggests the possibility that the removal of an unrecognized extrinsic exciting factor is an explanation for this rate of spontaneous remissions (19).

In addition to these extrinsic factors there is considerable evidence that intrinsic factors are also involved in the final development of the disease. Its occurrence in

previously healthy individuals, usually fecund females, following a respiratory infection or the administration of some drug, is difficult to explain. It is now recognized that there is a well-substantiated family history in patients with idiopathic systemic lupus erythematosus (20, 21). Because of this the term "lupus diathesis," or state of altered reactivity, has been proposed. In a recent review of this concept Holman pointed out that many abnormal immunologic reactions occur in the idiopathic form, including auto-immune reactions (1). To him this suggested an abnormal reactive system for antibody synthesis wherein antibodies to normal cell constituents are elaborated by the host. It is possible that drugs merely act as the inciting agent, or trigger mechanism, for this abnormal antigen antibody reaction.

To this end it has been proposed that drugs combine with body proteins to form haptenes which may be treated as foreign protein by the host with resultant antibody formation (15). Thus, systemic lupus erythematosus may be a "hyperergic" state which varies greatly in degree because of the individuality of a given patient. Similarly, the agent or factor eliciting this state may vary from individual to individual. This proposition fails to explain, however, why the antibody elaboration system of the afflicted patient loses its normal limiting "markers" which serve as controls for normal antibody formation. The host antibody elaboration system seems to go awry with the resultant development of antibodies in the body fluids against many kinds of host tissue—the so-called auto-antibodies. As Burnet has postulated, it appears that the intrinsic mechanism of the host for producing antibodies as a normal host defense mechanism loses its ability to distinguish "self" from "non-self" cell types or antigens (22).

Contrary to the widely held belief that the "drug induced SLE-like syndrome" invariably resolves after withdrawal of the drug, Newton observed the occurrence of a fatal instance of this type of syndrome in a nine-year-old boy who had been receiving trimethadione for two years (4). Similarly, we have seen this in an eight-year-old Negro boy who succumbed to renal failure (2). Now that the reaction is being recognized more frequently, it is reasonable to assume that fatal instances of this reaction will be observed more frequently.

Though the etiology of systemic lupus erythematosus is still unknown, fragments of the puzzle are being pieced together slowly. Further understanding of the pathogenesis of the disease, however, must await the unraveling of the intricate mechanism of antibody formation and the factors influencing their action.

HOWARD L. HOLLEY, M.D., F.A.C.P.
Department of Medicine
The University of Alabama Medical Center
Medical College of Alabama
Birmingham 3, Alabama

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Physician as Patient

FEW EXPERIENCES are more valuable to the physician than the experience of being a patient himself. Such an episode is worth a thousand lectures on the care of the patient. The Editor has recently undergone this salutary experience (repair of an inguinal hernia brought on by carrying all those manuscripts!). It has been a potent reminder of the world as seen by the bedridden patient, hospital life from the point of view of the underdog—under the sheet, that is. This is an educational opportunity that the physician should take advantage of if the Fates happen to send it his way.

Those of us who go about our busy daily lives enjoying health easily forget the changed perspective of the sick-room. Those four walls limit the mental, as well as the physical, horizon. Pain, that great leveler of all men, further narrows the introspective tunnel-vision—not so much the severe pain that can be suppressed by medication as the minor pain that merely nags. This is the pain that crowds in on one's thoughts awake or nibbles away the relaxation sought in rest or sleep. Then indeed the minor things become major, then the mirror is distorted. The seemingly endless delay until the bell is answered, the interminable wait on the flinty stretcher in the hall, the suspenseful wait—will they remember?—for that early morning cup of coffee: these are items that stretch out the scale of time. By the same token, the little acts of kindness illumine the dreary day: those extra five minutes of sympathetic understanding and complete attention of one's doctor, that unexpected letter or visit from a friend, that extra punching-up of pillows by the smiling angel in the white cap. All these diminish the importance of the crack in the ceiling.

In the long reaches of the night when the uncertainties of the future and the unpleasantnesses of the moment loom large, when every muscle and joint makes itself known with aching intensity, what price an extra back rub—if you could get it?

And then there is the loss of many of the personal privacies of life: for example, that pubic and perineal "prep" executed in the dead of night halfway between the last enema and the first step toward anesthesia. Few procedures involve a greater surrender of personal dignity! More to the point, few procedures, short of the *scheduled* surgery, require greater trust in the manual dexterity of one's fellow man as he, the orderly, wields the razor around one's most vulnerable parts—a keenly perceived Achille's heel located amidships (*there* is a mixed metaphor for you).

The bedpan, of course, is a subject for joking—except when you yourself are trying to use it. For most male patients, at least, this is the moment of anguish, a contortion of limbs, a snapping of synapses, a re-channeling of a familiar stream into an unfamiliar course. Happy the patient whose physician orders a commode; happy he who can totter to his feet and work with gravity instead of against it. Thus do routine activities, in health performed without thinking, in sickness imperatively intrude on consciousness. These are but a few of the obstacles that the patient must overcome to maintain his perspective on life, these are but a few of the reasons why most patients ask, no matter how prematurely, "When can I go home?"

The physician as patient is uniquely able to gain insight into his own medical problem, insight that may be of benefit both to himself and to his attending medical colleague (1). But of more importance to the future professional activities of the physician-patient is the lesson learned of the physical, mental, and spiritual struggles that daily are the lot of the patient in the sick-room. And especially does he learn the importance of his, the physician's, equanimity and compassion to the successful outcome of these struggles. Surely here, experience, if it comes his way, is the physician's best teacher.

J. R. E.

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BOOKS

Book Reviews

The Human Adrenal Gland. By Louis J. Soffer, M.D., F.A.C.P., Ralph I. Dorfman, PH.D., and J. Lester Gabrilove, M.D., F.A.C.P. 591 pages; 24 × 16 cm. Lea & Febiger, Philadelphia, 1961. Price, $18.50.

One entertains hopes, on opening a book entitled "The Human Adrenal Gland," that the wildly proliferating newer information relating to this organ will have been reduced by creative scholarship to the essentials required by the physician. If it cannot be said that the authors have succeeded in doing this, it should be said too that the task is appallingly difficult.

The treatment of the adrenal medulla furnishes a fair example of the book's principal weakness. The central fact of significance about the medulla is surely its very close relation to the sympathetic nervous system; and it seems that the presentation might well be built throughout upon this relationship—embryological, functional, and chemical. But the organization rests here on the relatively trivial fact of anatomic marriage of the adrenal cortex and medulla, with disruptive consequences. Here, as elsewhere in the book, disproportionate attention is allotted to admittedly important chemical discoveries of the past decade. It is quite wrong to say, as the authors do on page 117, that "the physiology of the adrenal medulla is essentially the study of the pharmacology of epinephrin and norepinephrin"; and the important subject of the physiologic control of adrenal medullary secretion is in fact slighted.

Conversely, other portions of the book are replete with detail of doubtful utility. The better part of ten pages is devoted to the meaning of various abnormalities of pituitary basophils to Cushing's syndrome, a notable ex-controversy; while in Chapters 2 and 3 the adrenal cortical steroids are reviewed in such detail, and references to original papers in this field so darken the pages, that one recalls with difficulty that the cortical hormones of vital importance for normal human physiology number exactly two.

Errors have crept in, including some hardy perennials of a vanished era. The idea that acute adrenal insufficiency is due essentially to sodium loss in the urine, repeatedly disproven during the past twenty-five years in man and other species, is reprieved in the opening pages of Chapter 6. "Metabolic craniopathy" also receives respectful consideration. If, as stated on page 94, testosterone may be the major androgen responsible for the manifestations of congenital virilism, the relevant evidence should certainly be furnished.

The work thus presents the aspect rather of a compendium than of an organized treatise. Doubtless the difficulties inherent in co-authorship, particularly perhaps embracing chemists and physicians, are in part responsible. The eminence of the authors is a sufficient warranty of the profusion of valuable material furnished in the areas of their respective special competencies. The volume will be welcomed by internists and endocrinologists as an accessory compilation and source of references up to 1959; particularly helpful is the review of recent advances in the study of hirsutism and related syndromes in young women. The authors can scarcely be blamed because the chapter on aldosteronism is already out of date.

A. Gorman Hills, M.D.

The Cardiac Arrhythmias. A Guide for the General Practitioner. By Brendan Phibbs, M.D. 128 pages; 25.4 × 17.5 cm. The C. V. Mosby Company, St. Louis, 1961. Price, $7.50.

In the words of the author, this book was written "to teach physicians who are not cardiologists to diagnose and treat cardiac arrhythmias." From the *Foreword* we understand that it is directed toward a special group of the medical profession, namely, the general practitioner, the anesthesiologist, and the surgeon who frequently are confronted with cardiac arrhythmias, yet who, because of their particular type of practice, do not have the opportunity to gain a complete understanding in the field of electrocardiography. Very few of the books which have been written on heart

disease and electrocardiography in recent years deal exclusively with cardiac arrhythmias, as does this work.

The book is divided into sections on anatomy and physiology (four pages), electrical registration of the heart beat (three pages), abnormal mechanisms as registered in the electrocardiogram (sixty-eight pages), clinical diagnosis (two pages), and exercises (fifteen pages). Much space is taken up with half or full page diagrams of cross sections of the heart which are used to demonstrate abnormalities of electrical conduction and arrhythmias. These are highly simplified and too numerous.

Because of its brevity the book is easy to read. The physical make-up is attractive, the diagrams and electrocardiograms are very well reproduced, and the index is good.

The author is a cardiologist and electrocardiographer. He seems qualified to write about this subject, though he has made no special contribution to the field and his book certainly contains no new information which is not available in other more sophisticated and complete works on heart disease and electrocardiographic diagnosis.

For the physician who needs a brief and very unsophisticated approach to cardiac arrhythmias, such as the group to whom it is directed, this book should be useful. It is not a reference to which one should turn to learn electrocardiography or to develop a broad knowledge of cardiac arrhythmias. It is not recommended as a source of information for the medical student or internist nor for the house officer and physician with special interests in cardiology.

JOSEPH C. ROSS, M.D.

Clinical Disturbances of Renal Function. By ABRAHAM G. WHITE, M.D. 25 × 17 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $10.50.

Actualités Néphrologiques de l'Hôpital Necker 1961. Introduction by Professor JEAN HAMBURGER. 312 pages; 25 × 16.5 cm. Éditions Médicales Flammarion, Paris, 1961. Price, NF 58, 50.

Despite the wealth of American and British contributions to renal physiology and pathology, we have in the English language no definitive textbook of renal disease. Dr. White's book might have filled this gap, but it has not.

The author's aim, most laudable, was to relate current views of abnormal renal function and of the pathogenesis of renal lesions to the clinical picture of renal disease. He has tried, as well, to make his book a practical one by presenting therapies for the disorders he discusses. But though his aims have been reached in some sections of his text, he has not given us a fully satisfying book.

First, and paradoxically, the book is long-winded despite its relatively modest length of four hundred-odd pages. Many of the chapters open with preludes of generalities, apparently designed to pose the problems to be considered in the following pages. But these preludes only postpone the getting down to facts. In some chapters, one wonders what happened to the kidney, for example, in the long discussion of hepatic disease, in the chapter on *Hormonally-Induced Disturbances of Renal Function,* and in the nine pages on the elements of human genetics.

These examples of an author's failing to "murder his darlings" might be discounted if the reader got adequate help where he needs it, in the problems that are most difficult in the clinic. But the diagnosis of unilateral renal disease, the differentiating of primary aldosteronism from that secondary to severe hypertension of other causes, the treatment of hyperkalemia in acute renal failure, the distinguishing of compulsive water drinking from other polyuric syndromes—all these presentations, and others, are sketchy and clearly inadequate. The problems in the diagnosis of hyperparathyroidism are hardly developed, notably the several hazards in the use of the tubular resorption of phosphate as a diagnostic test. In the discussion of renal stone formation, a number of clinically significant causes have been omitted. Cystinuria is confused with a completely unrelated disorder, cystinosis. The use of low solute-yielding diets is not included in the treatment of nephrogenic diabetes insipidus. And though bibliographies are supplied, the references are not well tied to the text, leaving the reader to guess where to go for what supplementary help.

Nor can it be said that Dr. White writes good prose. He has succumbed to the current vogue for "parameter," a term which has recently become a carry-all for what we used to call "variables," "tests," "estimates." Note these examples of lingo: "The presence of hypertension and renal insufficiency requires particularly careful observation when the steroid hormones are used. Should these parameters show marked deterioration . . ." (p. 61) ". . . the responsible etiological diagnosis . . ." (p. 87). Criticism of literary style is not a popular occupation in the United States, but remember

that clarity of thought and precise expression are sisters.

To what sources can the internist go for an adequate survey of kidney disease? Unhappily, he can find no single, completely adequate text in English. If he is rusty-minded in this area, he might first turn to de Wardener's *The Kidney. An Outline of Normal and Abnormal Structure and Function.* Here is a book admittedly sketchy in some details but admirably succinct and clear. But for a résumé of the most recent developments in knowledge of renal disease, other sources are needed. Discrete topics are presented in the *Yearbook of Medicine* and *Annual Review of Medicine,* but more general summaries can be found in the proceedings of occasional symposia, such as *Recent Advances in Renal Disease* (reviewed in the *Annals,* August 1961).

The English-reading physician who has a special interest in renal disease could very well use an equivalent in his language of *Actualités Néphrologiques 1961.* This annual summary of a large variety of topics in renal function and disease comes from the Metabolic Disease Clinic of Professor Hamburger in Paris. Almost half of the papers in this number deal with various experimental and clinical aspects of glomerulonephritis, and the rest range through such varied topics as anemia in renal disease, the functional study of renal acidosis, renal biopsy in essential hypertension, and the treatment of gout complicated by renal lithiasis.

A satisfactory textbook of renal disease will now probably have to be a multi-authored work, for the day has passed when any but the most brilliant and industrious author could hope to stay afloat in the torrent of papers from clinic and laboratory.

EDWARD J. HUTH, M.D.

Clinical Haematology. By ROBERT DUNCAN EASTHAM, B.A. (Cantab.), M.D. (Cantab.), D.C.P., DIPL. PATH. 158 pages; 18 × 10 cm. The Williams and Wilkins Company, Baltimore, exclusive U. S. agents, 1961. Price, $4.00.

This soft-covered pocket size book is not a treatise on clinical hematology but an interpretation of hematologic data. It offers very little information on clinical pictures of the various hematologic diseases, but the various causes of abnormal hematologic findings are given. The discussion of iron metabolism and the actions of vitamin B_{12} and folic acid are adequate.

The section on blood coagulation is good for someone who wants a quick review of the field. To the nomenclature of blood-clotting factors, Factor X (Stuart-Prower factor) should be added.

In any book that lists the diseases associated with various laboratory pictures, a few omissions are usually noted. For example, in this book polyarteritis is left out of the list of causes of eosinophilia. And the recovery phase of agranulocytosis is omitted among the causes of a monocytosis.

This little volume may be useful for medical students and house officers as a handy, quick reference for help in interpreting the laboratory findings of their patients.

HAROLD WURZEL, M.D.

Symposium on Anticoagulant Therapy—Report of the Proceedings. Edited by Sir G. W. PICKERING, M.A., D.SC., M.D., F.R.C.P. (Lond.) 284 pages; 22.5 × 15 cm. Harvey & Blythe Ltd., London, 1961. Price, 21 s.

The nineteen papers given at the symposium on anticoagulant therapy held at the Royal Society of Medicine on November 18 and 19, 1960, form the body of this excellent book; it should be read by everyone who deals with anticoagulants or plans to do so in the future.

The symposium started with a review of the action of oral anticoagulants on the blood coagulation mechanism. Papers were then presented on the methods of controlling the dosage of the drugs used. Most of the speakers prefered Owren's thrombotest to the Quick one-stage prothrombin test. On the other hand, most of the discussants had been using Quick's test.

The advantages, disadvantages, indications, and contraindications in anticoagulant therapy for various thromboembolic diseases were adequately discussed. Large series of patients were reported on along with the differing rates of mortality between those given anticoagulant therapy and those not treated.

The time spent on the problems of long-term anticoagulant therapy was much greater than that spent on short-term therapy. The administrative problems and costs as well as the clinical problems of this type of therapy were excellently reviewed.

It is a credit to the editor and publishers that this book is available so soon after the meetings were held. The report of this symposium should be in the library of every physician who has patients on anticoagulant therapy as well as those in control of the laboratory procedures.

HAROLD WURZEL, M.D.

Psychopathology of Aging. Edited by PAUL H. HOCH, M.D., and JOSEPH ZUBIN, PH.D. 321 pages; 22.5 × 14.5 cm. Grune & Stratton, Inc., New York, 1961. Price, $9.75.

Papers read at the fiftieth annual meeting of the American Psychopathological Association in February 1960 make up the text of this book. Statistical considerations by Marks (based on life insurance data), and by Pollock, Locke, and Kramer (based on a variety of institutional data), show that the incidence of mental diseases in old people, which has risen regularly and sharply in this country for the first five decades of this century, leveled off in the decade 1950 to 1959 and may even be declining. Marks mentions improvements in general medical care; Pollock gives some credit to improved conditions in living; all remark on the great variations in styles of diagnosis and disposal throughout the United States. There is less certainty that vascular diseases are the prime factors in the psychoses in old people, and the entity, chronic brain syndrome, gains favor. Among old people who are in institutions, the syndrome is mildest in those in old-age homes, where socioeconomic reverses are common precipitating factors. It is moderate in those in nursing homes where somatic diseases are outstanding; and it is most severe in those in state mental hospitals, where both somatic and brain diseases are well advanced.

A paper by Wallach and Kogan is a model of sound psychological research. One by Katz, Neal, and Simon is equally a model for clinical studies. Two papers are outstanding, "Concepts of Aging," by Franklin N. Arnhoff, and "Research on the Psychology of Aging: Concepts and Findings," by James E. Birren. Birren reviews the many variables that are involved in aging processes and gives evidence that a factor of "general intelligence" is not affected by advancing years. Another factor, related to use and disuse, is more clearly age-related, and this may have clinical interest. Arnhoff warns that, in view of the complexity of the somatic and psychic systems and their great capacities to grow and to make adjustments, researches too narrowly designed are likely to reach false conclusions. Research workers are not exempt from the general prejudice against age. What is interpreted by some as "withdrawal" or "deterioration" may be growth change in values or goals or attitudes —an ability to organize behavior strategically, as Welford puts it.

This book merits careful reading by physicians who are concerned with how they may better understand and care for their aging patients. Their "psychopathology" is not as general nor as progressive nor as resistant to therapy as it has been assumed to be.

ROBERT T. MONROE, M.D.

Inflammation and Diseases of Connective Tissue. A Hahnemann Symposium. Edited by LEWIS C. MILLS, M.D., and JOHN H. MOYER, M.D. 900 pages; 25 × 16.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $16.00.

This symposium is an ambitious undertaking when one considers that an entire symposium could easily be devoted to either inflammation or connective tissue, or, in fact, to an aspect of either. The extent of the symposium is evidenced by the fact that close to one hundred and fifty participants were involved, and approximately one hundred and twenty papers were presented. In an undertaking of this scope it is inevitable that the stature of the authors and the quality of their papers will vary considerably. Nevertheless, the principle that top men generally produce top work held true. Generally, the quality and ability of the participants were of the highest order; thus, most of the papers were stimulating.

Essential organization of the presentation was made possible by a division of the symposium into nine sections. Papers of interest only to the clinician were presented, as well as papers of interest only to the researcher, in the expectation that each would be stimulated by the work of the other.

Some sections of the symposium are of value primarily to investigators, some, to clinicians; yet the book should be of interest to anyone working in the field, regardless of his particular area of study.

E. A. HILDRETH, M.D.

Ciba Foundation Study Group. No. 8. Problems of Pulmonary Circulation. A. V. S. DE REUCK, M.SC., D.I.C., A.R.C.S., and MAEVE O'CONNOR, B.A., editors for the Ciba Foundation. 96 pages; 19 × 13 cm. Little, Brown and Company, Boston, 1961. Price, $2.50.

From time to time the Ciba Foundation has assembled leaders in some field of research for a day-long intensive discussion of their specialty. This little book on *Problems of the Pulmonary Circulation* records the six papers read and the debate elicited at a recent conference of this type.

Much of the value of this effort lies in the informal exchange. The main ideas in the papers, for example, C. T. Dolley's use of radioactive carbon dioxide to measure regional blood flow, and I. deBurgh Daly's concepts of the nervous control of the pulmonary circulation, are available in the journal literature. The worker in the area of cardiopulmonary physiology, however, will enjoy sitting with the discussants as they erect hypotheses, while the general medical reader will sense some of the hazards of life on the frontier.

This booklet is recommended for those wishing to supplement their knowledge of the behavior of the pulmonary circulation.

ROBERT W. CARTON, M.D.

Oncogenic Viruses. Vol. II. International Series of Monographs on Pure and Applied Biology. LUDWIG GROSS, M.D. 393 pages; 23.5 × 16.5 cm. Pergamon Press, Oxford, 1961. Price, $12.00.

Dr. Gross discusses the experimental and naturally occurring benign and malignant tumors of viral etiology. Because the neoplasms in which the relationship to a virus is proven occur in amphibian, avian, and lower mammalian species, the major part of this book is concerned with a discussion of such tumors. In each instance there is presented an interesting historical background, as well as current research developments in the demonstration of various oncogenic viruses. The author gives a detailed presentation of his own experiments demonstrating the viral transmission of mouse leukemia and tumors caused by the mouse parotid tumor (polyoma) virus.

The last chapter summarizes studies carried out in the search for oncogenic viruses in man, some of which have yielded suggestive, but not conclusive, results. The author discusses his view that the viral etiology of human tumors at the present time is a reasonable "working hypothesis."

This book contains an excellent bibliography in the field of tumor virus research and presents a lucid description of the multiple experimental data now on hand in this rapidly progressing branch of oncology.

ESTHER F. HAYS, M.D.

Psychosomatic Aspects of Paediatrics. Study Group of the Society for Psychosomatic Research Held at the Royal College of Physicians, May, 1959. Edited by RONALD MACKEITH and JOSEPH SANDLER. 155 pages; 26 × 18 cm. Pergamon Press, New York, 1961. Price, $8.50.

Gathered into this book are the Proceedings of the Society for Psychosomatic Research, from meetings held at the Royal College of Physicians in 1959. The purpose of these meetings was to offer pediatricians "an opportunity for the discussion of clinical problems, . . . of current psychological and psychopathological theories, . . . some rather philosophical aspects of the idea of 'causation' in the field, and a session on the planning of research." Both the formal papers and subsequent discussions are presented and both are eminently worth recording.

As is evident, the scope of the meetings was broad, so it is fortunate that the papers can now be read at leisure. Among the many rewards will be the lucid exposition of ethology by Bowlby and of identification by Sandler, the hard core analysis of research problems by Abercrombie and by Reid, the rich clinical presentations of Frankl. The discussions of encopresis and of recurrent pains are exceptionally comprehensive; they serve as models of the fruitfulness of the psychosomatic approach when it is applied to problems of definition, etiology, and therapy. To the more experienced workers in the psychosomatic field, the discussion sections might well prove more exciting than the formal presentations. What is impressive here is the openness to the psychosomatic approach, the total absence of hostility to psychiatry and to psychoanalysis which is such a stumbling block to interdisciplinary rapprochement.

As with all symposia, this one has certain weaknesses. The presentation of learning theory is needlessly detailed and burdened with issues of no more than parochial interest. Bowlby's enthusiastic exposition of ethology contains no hint of the critical second look which is taking place on this side of the Atlantic, while Sandler by-passes the fascinating problem of transference in pediatricians in contrast to other medical specialists. Finally, some pointed crosscultural questions were consistently ignored, and the symposium lacked the kind of perspective which comes from knowledge of different social patterns.

A special word should be said about the section in which Anna Freud answers questions. This should be required reading for every pediatrician wondering whether to adopt the psychosomatic orientation. Miss Freud clearly states that the study of mental life is not for

the dilettante, and psychology should not be regarded as a repository of answers to questions which hound the pediatrician in his practice. The psychosomatic approach demands expertness and a high tolerance for searching. Incidentally, Miss Freud's answers to questions about problems of feeding, sleeping, crying, and medication are as sensible and apposite as can be found.

One final remark: This symposium was organized on the basis of comprehensiveness, but it might have been even more successful if it had been organized on the basis of strict relevance to pediatrics. Clearly the entire range of developmental psychology, of psychosomatic theory, and of research cannot be covered, and the pediatrician is either baffled by complexity or presented with an incomplete sample of theory and research strategies. More important is the fact that much of current thinking on personality development is not particularly relevant to the psychosomatic aspects of pediatrics, and much of psychosomatic theory is vague and unsatisfactory. Interestingly enough, in the unstructured question-and-answer session with Miss Freud, the pediatrician asked about feeding, sleeping, crying, etc.—the traditional problems in the field. A case can be made that pediatricians should be encouraged to stick close to these problems, and that theory and research should be introduced primarily for what light they can shed on understanding them.

In sum, this book presents a comprehensive view of the psychosomatic approach to clinical problems, of developmental and psychosomatic theories, and of psychosomatic research. It should be particularly valuable to those pediatricians curious to learn the rewards and, equally important, the frustrations of including psychological factors in the evaluation of the children they see. The more experienced workers in the field will be heartened by the vitality of the discussions; hopefully the excitement generated here will be contagious, so that the touch-and-go relationship between pediatrics and psychology can grow into a durable companionship.

CHARLES WENAR, PH.D.

The Premature Baby. 5th Ed. By V. MARY CROSSE, O.B.E., M.D. 21.3 × 14.3 cm. Little, Brown and Company, Boston, 1961. Price, $7.00.

The appearance of five editions in sixteen years is sufficient evidence that this book has been well received. The present edition appears to represent a true revision, with new material and new references. It is essentially a record of the author's extensive personal experience, with brief but adequate discussion of the pertinent literature. More complete reviews are provided for important topics such as respiratory distress, hyperbilirubinemia, and retinopathy. Home care of the premature infant is discussed in considerable detail for the benefit of those areas where hospital birth and after-care are not always available. Hospital care is well covered, including the important practical details of feeding and other procedures, and there is an excellent discussion of aseptic techniques. The major problems are included in a chapter on *Complications Liable to Occur*. The last chapter and the *Appendix* contain much useful statistical information and a valuable discussion of long-term prognosis, based on data of the author and others from Birmingham.

One finds little cause for disagreement and only occasional difference of opinion. The advisability of masks for nurses might be questioned. The allowance of fifty square feet per cot and thirty square feet per closed incubator, as recommended, is sufficiently large that some benefit might be expected. Unfortunately it is difficult to devise a study which would prove or disprove the value of such expensive use of space. The proper attitude toward low temperatures remains unclear. Dr. Crosse advises using sufficient external heat to keep the rectal temperature above 95 F. Many small babies seem to do well at lower temperatures and are thus spared the risks of overheating. Chilling due to cold environment is another matter and may be dangerous. Resuscitation by mask and bag is not mentioned. Intragastric oxygen is described as being valuable in some circumstances, although the evidence for its value is questionable. The occasional need for oxygen concentrations above 35 to 40% is mentioned but might have been made clearer. With rare exceptions, generalized cyanosis would seem to provide adequate assurance that the plasma oxygen tension is too low. The Beckman oxygen analyzer is more convenient than the apparatus described. The critical level for serum bilirubin remains indefinite and vexing. Blood transfusion is advised for hemoglobin below 7 grams; even lower levels are well tolerated provided the baby is otherwise well.

These minor differences of opinion are of little importance in relation to the general

value of the book. It will be of great interest to all those who are concerned with the care of premature infants and it is recommended to their attention.

F. H. HARVIE, M.D.

The Newborn Child. By DAVID G. VULLIAMY, M.D. 163 pages; 21 × 14.5 cm. Medical Book Department, Little, Brown and Company, Boston, 1961. Price, $6.00.

In 150 pages of text, Dr. Vulliamy has presented a dependable guide to the more common aspects of newborn care. As indicated in the *Preface,* the book is intended for recent graduates or others without special training or extensive experience in the care of newborn infants. The presentation is clear and practical throughout and is obviously based on a thorough knowledge of the subject. The photographic illustrations, and a few drawings, are excellent.

A surprising amount of information is included, with only minor occasion for disagreement. Positive-pressure resuscitation through a mask is mentioned but merits more consideration. One might question the statement that a fine watery mist is of "proven value" in the treatment of the respiratory distress syndrome, and we have been disappointed with the use of cortical steroids for babies with sclerema. We have not felt it worthwhile to look for staphylococcal carriers.

The recommendation for nursery temperatures of 65 to 70 F makes pleasant reading during summertime in Philadelphia. It is not surprising that rectal temperatures of less than 100 are accepted here as normal whereas Dr. Vulliamy sets the limit at 99. Perhaps this difference explains why the reviewer does not see "dehydration fever."

The book is admirable for the purpose intended, and pediatricians will enjoy comparing opinions with the author.

F. H. HARVIE, M.D.

Sterility. Office Management of the Infertile Couple. Edited by EDWARD T. TYLER, M.D. 425 pages; 20.5 × 14.3 cm. The Blakiston Division of McGraw-Hill Book Company, Inc., New York, 1961. Price, $12.50.

This volume is a compilation of a series of lectures given over the years by sixteen individuals in postgraduate extension division courses of the University of California (Los Angeles) Medical Center. The contributors are authorities on the wide range of subject matter included.

In addition to the usual subjects to be found in books on sterility, such as management of infertility of both the male and female, there is an excellent chapter on abortion and an outstanding discussion on the control of fertility.

As might be expected with numerous contributors, the quality of the writing varies somewhat, but all is at least good, and in certain instances, superb.

The primary usefulness of this book will be for those dealing with infertile individuals. However, endocrinologists may find the material on hormone assays valuable. Internists who have any interest in gaining a general background of some of the latest information on infertility will find this book authoritative, yet readable. The chapters on control of fertility and immunologic factors in infertility are fascinating reading for anyone.

ALAN RUBIN, M.D.

Book Notices

Cancer Prognosis Manual. By ARTHUR G. JAMES, M.D., F.A.C.S. 74 pages; 27.5 × 21.5 cm. American Cancer Society, Inc., New York, 1961.

A physician who cares for patients with malignancies needs accurate prognostic data. When he must present the outlook for the patient to his relatives, he owes them a sound estimate.

Prognostic data are scattered widely in journals and monographs and are not easy for the physician to dig out. Dr. James has prepared this manual for distribution by the American Cancer Society, and it should be most useful to all physicians concerned with neoplastic disease.

For each type of lesion (anatomical site), a table presents five and ten-year survival rates and such rates as they depend on treatment, stage of the lesion, and histologic type. The tables include the numbers of cases on which the survival percentages are based, and they are followed by the reference sources used in gathering the data.

E. J. H.

The Pfizer Handbook of Microbial Metabolites. By MAX W. MILLER, PH.D. 772 pages; 23.5 × 16 cm. McGraw-Hill Book Company, Inc., New York, 1961. Price, $15.00.

The explosive growth of research in microbial metabolism in the past two decades has been due largely to the unending efforts of drug companies to find new antibiotics. These efforts and related research in academic laboratories have piled up mountains of data on the varieties of compounds produced by bacteria, molds, fungi, and lichens and on the metabolic pathways leading to these compounds. Descriptions of metabolites in this *Handbook* are grouped by structural similarities into separate chapters. Such groupings include those of carotenes, anthraquinones, amino acids, polypeptides, indoles, purines, and so forth. Each description of a metabolite includes physical and clinical properties, structural formula, the microbial sources, and literature references. A long *Addendum* includes data published through 1960.

The three indices present metabolites by chemical name, empirical formulas, and the microorganisms producing these metabolites.

E. J. H.

Diagnostik der Neuroendokrinen Krankheiten und Ihre Pathophysiologischen Grundlagen. By M. JULESZ and I. HOLLO. 858 pages; 24.5 × 19 cm. Academiai Kiado, Budapest, 1961.

Diagnostic Methods in the Neuroendocrine Diseases and Their Pathophysiological Basis first presents an account of the use of the medical history, physical examination, laboratory tests, and roentgenography in the study of patients with these disorders. The second part of the text discusses diagnostic approaches to specific endocrine problems. The text is generously illustrated with photomicrographs, roentgenographs, pictures of characteristic patients, and diagrams.

E. J. H.

The Myocardium—Its Biochemistry and Biophysics. Edited by ALFRED P. FISHMAN, M.D. 227 pages; 27.5 × 20 cm. American Heart Association and New York Heart Association, Inc., New York, 1961. Price, $2.50.

This group of papers on the ultrastructures of the heart and the biochemical basis of myocardial contraction and electrical activity first appeared in a supplement to *Circulation,* August 1961. An index to these reprinted papers has been included in this re-issue.

E. J. H.

Hypertension. Vol. IX. Chemical and Hormonal Factors. Proceedings of the Council for High Blood Pressure Research, American Heart Association, November, 1960. Edited by FLOYD R. SKELTON, M.D., PH.D. 806 pages; 27.5 × 20 cm. American Heart Association, Inc., New York, 1961. Price, $2.50.

Papers originally published in the May 1961 number of *Circulation Research* have been gathered into this volume. The papers are listed in a table of contents but have not been indexed.

E. J. H.

Vaccins et Serums. By P. CHASSAGNE. 404 pages; 24.5 × 16 cm. G. Doin & Cie., Paris, 1961.

The prophylactic and therapeutic uses of anti-sera and vaccines for microbial diseases are summarized in this French monograph. A table of required and recommended vaccina-

tions for travelers in various areas of the world is appended to the text.

E. J. H.

A Practical Outline for Preparing Medical Talks and Papers. By ROBERT M. ZOLLINGER, M.D., WILLIAM G. PACE, III, M.D., and GEORGE J. KIENZLE, B.A. 57 pages; 23.5 × 15.5 cm. The Macmillan Company, New York, 1961. Price, $1.95.

Lectures hold audiences more because they have been properly prepared than because of their content. Many of the devices and principles used by effective speakers are set forth clearly and simply in this manual. Were they used more widely, fewer audiences would prefer Morpheus to the lecturer.

E. J. H.

Essentials of Histology. 4th Ed. By GERRIT BEVELANDER, PH.D. 288 pages; 25 × 17 cm. The C. V. Mosby Company, St. Louis, 1961. Price, $5.75.

Dr. Bevelander's presentation of the elements of human histology is illustrated largely with drawings and diagrams; photomicrographs have been used sparingly. His text is not supplemented with references or bibliographies.

E. J. H.

Books Recently Received

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be selected for review, but it is not possible to discuss all of them.

Actualités Néphrologiques de l'Hôpital Necker 1961. Introduction by JEAN HAMBURGER. 312 pages; 25 × 16.5 cm. Éditions Médicales Flammarion, Paris, 1961. Price, NF 58, 50.

Atlas of Surgical Operations. By ROBERT M. ZOLLINGER and ELLIOTT C. CUTLER. 237 pages; 37.5 × 26.5 cm. The Macmillan Company, New York, 1961. Price, $18.00.

Basic Biochemistry. By M. W. NEIL, PH.D. 360 pages; 22.5 × 14.5 cm. J. B. Lippincott Company, Philadelphia, 1961. Price, $6.75, North American market.

Clinical Hematology. 5th Ed. By MAXWELL M. WINTROBE, M.D., PH.D., D.SC. (HON.) 1,186 pages; 26 × 18 cm. Lea & Febiger, Philadelphia, 1961. Price, $18.50.

Development and Structure of the Cardiovascular System. An American College of Cardiology Monograph. Edited by ALDO A. LUISADA, M.D. 247 pages; 26 × 18 cm. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1961. Price, $9.95.

Essentials of Histology. 4th Ed. By GERRIT BEVELANDER, PH.D. 288 pages; 25 × 17 cm. The C. V. Mosby Company, St. Louis, 1961. Price, $5.75.

Hormones in Blood. Edited by C. H. GRAY and A. L. BACHARACH. 655 pages, 23.5 × 16 cm. Academic Press, Ltd., London, 1961. Price, $20.00.

Human Genetics: Principles and Methods. By C. C. LI, PH.D. 218 pages; 22 × 15.5 cm. McGraw-Hill Book Company, Inc., New York, 1961. Price, $8.50.

The Myocardium—Its Biochemistry and Biophysics. Edited by ALFRED P. FISHMAN, M.D. 227 pages; 27.5 × 20 cm. American Heart Association and New York Heart Association, Inc., New York, 1961. Price, $2.50.

The National Vitamin Foundation. 1960 Annual Report. 131 pages; 23 × 15.5 cm. The National Vitamin Foundation, Inc., New York, 1961.

Neurophysiology. By THEODORE C. RUCH, PH.D., HARRY D. PATTON, PH.D., M.D., J. WALTER WOODBURY, PH.D., and ARNOLD L. TOWE, PH.D. 521 pages; 26 × 17 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $10.00.

Nursing Home Administration. Training Materials for Administration of Nursing, Boarding, and Mental Hygiene Homes for the Aged. By JOHN D. GERLETTI, ED.D., C. C. CRAWFORD, PH.D., and DONOVAN J. PERKINS, M.S. 472 pages; 25.5 × 18 cm. The Attending Staff Association, Downey, California, 1961. Price, $6.50.

Oncogenic Viruses. Vol. II. International Series of Monographs on Pure and Applied Biology. By LUDWIG GROSS, M.D. 393 pages; 23.5 × 16.5 cm. Pergamon Press, Oxford, 1961. Price, $12.00.

Pathology. 4th Ed. Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P., F.C.A.P. 1,389 pages; 27.5 × 19 cm. The C. V. Mosby Company, St. Louis, 1961. Price, $18.00.

Problems of Estimating Changes in Frequency of Mental Disorders. Report No. 50. By THE COMMITTEE ON PREVENTIVE PSYCHIATRY. 64 pages; 22.5 × 15 cm. Group for the Advancement of Psychiatry, New York, 1961. Price, 75 cents (paper bound).

Psychopathology of Aging. Edited by PAUL H. HOCH, M.D., and JOSEPH ZUBIN, PH.D. 321 pages; 22.5 × 14.5 cm. Grune & Stratton, Inc., New York, 1961. Price, $9.75.

Respiration in Health and Disease. By R. M. CHERNIACK, M.D., S.SC., F.R.C.P. (C), and L. CHERNIACK, M.D., B.SC., M.R.C.P. (LOND.), F.R.C.P. (C), F.A.C.P. 403 pages; 24 × 16.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $10.50.

Survey Report: Cerebral Vascular Study Group, Institute of Neurological Diseases and Blindness, National Institutes of Health. 139 pages; 28 × 22 cm. Bardgett Printing and Publishing Company, St. Louis, 1961.

MEDICAL NEWS

Meetings

Jan. 18–20, 1962. American Society of Clinical Radiology, Arizona Biltmore Hotel, Phoenix, Arizona. Louis Shattuck Baer, M.D., 411 Primrose Road, Burlingame, California, Secretary.

April 1–6. American College of Allergists, eighteenth annual congress, Hotel Radisson, Minneapolis, Minnesota. John D. Gillaspie, M.D., Treasurer, 2141 14th Street, Boulder, Colorado.

April 9–13. American College of Physicians, Bellevue-Stratford Hotel, Philadelphia. Edward C. Rosenow, Jr., M.D., 4200 Pine St., Philadelphia 4, Executive Director.

April 28. American Society for Clinical Nutrition, Chalfonte Hotel, Atlantic City, New Jersey, Robert E. Hodges, M.D., Secretary-Treasurer.

April 30–May 2. American Academy of Pediatrics, Statler-Hilton Hotel, New York City. E. H. Christopherson, M.D., 1801 Hinman Ave., Evanston, Ill., Executive Director.

June 21–25. American College of Chest Physicians, 28th Annual Meeting, Morrison Hotel, Chicago, Illinois. Mr. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois, Executive Director.

International and Foreign Meetings

Jan. 22–24, 1962. First Inter-American Conference on Congenital Defects, The Statler Hotel, Los Angeles. Stanley E. Henwood, Executive Secretary, International Medical Congress Ltd., Room 3013, 120 Broadway, New York 5.

Feb. 17–24. Eighth Congress Pan American Medical Women's Alliance, Manizales, Colorado. Dr. Eva Dodge, President-Elect, 2124 W. 111th St., Little Rock, Ark.

Feb. 20–24. Seventh International Congress on Diseases of the Chest, New Delhi, India. Mr. Murray Kornfeld, Executive Director, 112 East Chestnut Street, Chicago 11, Ill.

Mar. 26–31. Health and Tuberculosis Conference, University College, Ibadan, Nigeria. Conference Secretary, The Chest and Heart Association, Tavistock House North, Tavistock Square, London, W. C. 1.

Apr. 9–12. Thirty-third Annual Meeting Aerospace Medical Association, Atlantic City, N. J. Dr. William J. Kennard, Secretary-Treasurer, c/o Washington National Airport, Washington, D. C.

April 23–25. Eighth Pan-American Congress of Gastroenterology, Hotel Roosevelt, New York. Charles A. Flood, M.D., Executive Secretary.

May 13–19. Fourth World Congress of Gastroenterology, Munich. Dr. G. A. Martini, Secretary, c/o Universitäts Krankenhaus, Eppendorf, Hamburg, Germany.

Sept. 9–15. International Congress of Pediatrics, Lisbon, Portugal. American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, Illinois.

Postgraduate Courses
The American College of Physicians

Schedule of Postgraduate Courses,

Fall–Winter, 1961–62

Course No. 5, Internal Medicine—Today's Problems in Diagnosis and Management, and Tomorrow's Projections, Ochsner Foundation Hospital, New Orleans, La.; A. Seldon Mann, M.D., F.A.C.P., and William D. Davis, Jr., M.D., F.A.C.P., Co-Directors; January 15–18, 1962.

Course No 6, Medical Genetics, The University of Michigan Medical School, Ann Arbor, Mich.; James V. Neel, M.D., F.A.C.P., Director; January 29–February 1, 1962.

Course No. 7, Pathologic Physiology of the Blood Dyscrasias, Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., F.A.C.P., and Edward H. Reinhard, M.D., F.A.C.P., Co-Directors; February 12–16, 1962.

Course No. 8, Symposia on Challenging Medical Problems, Baylor University College of Medicine, Houston, Tex.; Raymond D. Pruitt, M.D., F.A.C.P., Director; February 19–23, 1962.

For information and application blanks, please write directly to Edward C. Rosenow, Jr., M.D., Executive Director, The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

American Diabetes Association

Jan. 17–19, 1962. Tenth Postgraduate Course, "Diabetes in Review: Clinical Conference, 1962." Sessions of the first and third days will be at The Statler Hilton, Detroit; those of the second day will be at the University of Michigan, Ann Arbor. The American Academy of General Practice will give 19 hours of Category II credit for the course. Registration is open to Doctors of Medicine; the fee is $40.00 for members of the American Diabetes Association, and $75.00 for non-members. Additional data and registration forms may be secured from American Diabetes Association, 1 East 45th Street, New York 17.

Temple University School of Medicine and Hospital

Mar. 5–16, 1962. Postgraduate Course in Allergy. A continuous two-week course offered by the Departments of Allergy and Applied Immunology of the Temple University Medical Center and the Graduate School of Medicine of the University of Pennsylvania. Sessions will be held daily at the Temple University Medical Center from 9:00 AM to 5:00 PM. Tuition, $175.00; enrollment limited. Louis Tuft, M.D., is course director; George I. Blumstein, M.D., and Merle M. Miller, M.D., are associate directors. For brochure and application forms write to George Blumstein, M.D., Temple Medical Center, Philadelphia 40.

American College of Allergists

April 1–6, 1962. Graduate Instructional Course. This course will be held concurrently with the eighteenth annual congress at Hotel Radisson, Minneapolis, Minnesota. For information, write to John D. Gillaspie, M.D., Treasurer, 2141 14th Street, Boulder, Colorado.

Examinations and Licensure

American Board of Preventive Medicine. Written examination in public health, aviation medicine, and occupational medicine, Spring of 1962. Dr. Tom F. Whayne, 4219 Chester Ave., Phila. 4, Pa., Secretary.

American Board of Internal Medicine

I. Written Examination—October 15, 1962.
The closing date for acceptance of applications—May 1, 1962.

II. Oral Examinations:
New Orleans—January 28, February 1, 1962.
The closing date for acceptance of applications—December 15, 1961.
Philadelphia—April 3–7, 1962.
The closing date for acceptance of applications—January 2, 1962.
San Francisco—September 9–13, 1962.
The closing date for acceptance of applications—April 1, 1962.
Chicago—November 4–8, 1962.
The closing date for acceptance of applications—April 1, 1962.

Subspecialty oral examinations in Gastroenterology:
Ann Arbor, Michigan—March 26–27, 1962.
The closing date for acceptance of applications—February 1, 1962.

Columbia University College of Physicians and Surgeons

March 12–14, 1962. A symposium, "Basic Problems in Neoplastic Disease," will commemorate the fiftieth anniversary of the Institute of Cancer Research at Columbia University and the tenth anniversary of its affiliated clinical facility, The Francis Delafield Hospital. The symposium is open without fee to all interested workers in this field. For details and applications, write to the Institute for Cancer Research, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York 32, N. Y.

Three-Year Residency in Neoplastic Diseases

The Francis Delafield Hospital, affiliated with Columbia University College of Physicians and Surgeons, New York, offers a three-year residency program accredited by the American Board of Internal Medicine.

The first year includes general medicine consisting of ward service, hematology, cardiology, and diagnostic radiology. The second year includes training in either hematology or cardiology, and supervision of first year residents. The third year may be served as the chief resident or in a fellowship program. Opportunity to do clinical and laboratory investigations is available during the second and third years.

The program can be started July 1, 1962. The stipend depends upon individual experience, minimum, $3,380, and living quarters are provided in the hospital. Applications should be

addressed to Alfred Gellhorn, M.D., Director of Medicine, Francis Delafield Hospital, 99 Fort Washington Ave., New York 32, N. Y.

Endocrine Society

The forty-fourth annual meeting of The Endocrine Society will be held in Chicago, June 21 through June 23, 1962. Those desiring to present papers should send the original and four copies of the title and abstract, not later than February 15, 1962, to Leslie L. Bennett, Vice President, Department of Physiology, University of California Medical Center, San Francisco 22, California.

Louis Lefkoe Memorial Foundation

A prize essay contest sponsored by the Louis Lefkoe Memorial Foundation, under the auspices of the Pennsylvania Academy of Physical Medicine and Rehabilitation, is open to residents, interns, and medical students. Manuscripts must be submitted in triplicate before February 15, 1962. Address inquiries to Emery K. Stoner, M.D., F.A.C.P., Department of Physical Medicine, Hospital of the University of Pennsylvania, 3600 Spruce Street, Philadelphia 4, Penna.

United States Public Health Service Awards

A program designed to increase the number of career opportunities in medical research and teaching at universities, medical schools, and similar institutions throughout the country is announced by the United States Public Health Service. The program will be administered by the National Institutes of Health, and awards will be made to scientists of "superior potential and capability in the sciences related to health."

Two groups of awards are available. Research Career Awards are for experienced investigators and will be made in five-year increments. Research Career Development Awards are for younger investigators, and candidates for these awards must have had at least three years of related research or other professional experience following the doctoral degree. These are for initial periods of five years and are renewable up to five additional years.

Requests for applications or further information can be obtained from the Chief, Career Development Review Branch, Division of Research Grants, National Institutes of Health, Bethesda 14, Maryland.

World Rehabilitation Fund

A limited number of fellowships are available to physicians from other nations for postgraduate training in physical medicine and rehabilitation. These are for one year, but are renewable to a maximum of three years. Training is given in the Department of Physical Medicine and Rehabilitation, New York University Medical Center. Stipend will be $3,400.00 per year without room and board, with $1,900.00 to $2,900.00 per year when room and board are provided. Visas are sponsored by the New York University Exchange Visitors Program. Awardees must have had their credentials evaluated by the Educational Council for Foreign Medical Graduates, and must have passed successfully the examination of the Educational Council for Foreign Medical Graduates prior to applying for fellowship. Full details may be obtained from the World Rehabilitation Fund, 400 East 34th Street, New York 16, New York.

Johns Hopkins University School of Medicine

The Division of Clinical Pharmacology, Department of Medicine, Johns Hopkins University School of Medicine, offers a one to three year fellowship in clinical pharmacology to physicians who have completed a minimum of one, and preferably two or more years of house staff training. The fellowship provides clinical and laboratory experience relevant to the evaluation of drugs in man, plus biostatistical instruction. Emphasis is placed on methodology and controlled trials. Accepted candidates are considered post-doctoral fellows in the Department of Medicine and participate in certain clinical and teaching activities of the Department as a whole.

Applications may now be filed for the year beginning July 1, 1962, and for the year beginning July 1, 1963. Write to Dr. Louis Lasagna, Station 915, The Johns Hopkins Hospital, Baltimore 5, Maryland.

INSTRUCTIONS TO AUTHORS

MANUSCRIPTS: All papers should be typewritten on one side of the paper and double spaced (including references, figure legends, and footnotes). The original and one carbon copy should be submitted with duplicate copies of all figures and tables. A separate title page should include the following: title, subtitle (if any), author(s) and his (their) degree(s), F.A.C.P. (if Fellow of the American College of Physicians), city or town where the work was done, hospital or academic institution (if any), and necessary acknowledgment of financial sponsors.

The introduction should orient the paper in relation to its field and should state its purpose. The main sections (for example, RESULTS) should be identified by centered headings in capital letters. Indicate further subdivisions by side headings that are flush with the left-hand margin and one line above the text, by paragraph headings which should be indented on the first line of the paragraph and underlined, or by both. Extensive discussion should be separated from the presentation of the results. A succinct summary should state what was done, what was found, and what the findings are interpreted to mean. For guidance to sound grammar and clear style consult *The Elements of Style* by W. Strunk, Jr. and E. B. White, The Macmillan Co., New York, 1959.

ABBREVIATIONS, SYMBOLS, AND NOMENCLATURE: Abbreviations should conform as closely as possible to the *Style Manual for Biological Journals*, published in 1960 by the Conference of Biological Editors, Committee on Form and Style, American Institute of Biological Sciences, 2000 P Street, NW, Washington 6, D. C. Abbreviations should be kept to a minimum and preferably confined to tables; some frequently used abbreviations are listed at the bottom of this page. Generic names of drugs are preferred; a proprietary name may be given only with the first use of the generic name. *Webster's New International Dictionary* is the standard reference for spelling, compounding, and hyphenating. Cardiopulmonary nomenclature is used as given in "Standardization of definitions and symbols in respiratory physiology," *Fed. Proc.* 9: 602, 1950.

REFERENCES: These are to be cited consecutively in the text as numbers enclosed in parentheses *on the line of writing*, not as superscript numbers. At the end of each article references should be listed *in the numerical order in which they are first cited in the text*. This list should conform to the style of the *Index Medicus* but with end pagination and number and month of issue omitted, and should be punctuated as in the following examples.

For journal articles: Surname and initials of author(s) (in capitals), title of article (lower case), name of journal (underlined for italics), volume number, first page, year. Thus:

4. DOE, J. E., ROE, R. C.: What I know about it. *Ann. Intern. Med.* 27: 1590, 1960.

For books: Surname and initials of author(s) (in capitals), title and subtitle (caps and lower case, underlined for italics), edition (other than first), publishing house, city, year, page or chapter as specific reference. Thus:

5. OSLER, W.: *Aequanimitas. With Other Addresses to Medical Students, Nurses and Practitioners of Medicine*, 3rd Ed., H. K. Lewis and Co., London, 1948, p. 250.

For articles in books: Surname and initials of author(s) (in caps), title of article (lower case), chapter number (if any), first page of article, title of book (caps and lower case, underlined for italics), editor, edition (other than first), publishing house, city, year. Thus:

6. WINTERNITZ, M. C.: Notes on an attack of coronary artery disease, in *When Doctors are Patients*, ed. by Pinner, M. and Miller, B. F., W. W. Norton and Co., New York, 1952, p. 31.

References to articles in press must state name of journal and, if possible, volume and year.

Authors are responsible for bibliographic accuracy; authors must check every reference in manuscript and *again* in galley-proof.

FOOTNOTES: Footnotes to tables should be designated by symbols in the following order: *, †, ‡, §, ||, #, **, ††, ‡‡, etc. Footnotes to the text should be as few as possible and should be typed at the foot of the appropriate page separated from the text by a ruled line.

TABLES: These should be typed on separate sheets with number and title (in caps) and centered. Symbols for units should be confined to the column headings. Vertical lines should be omitted. All data should be checked for accuracy.

FIGURES: These should be submitted in photographic form (glossy prints) or as original india ink drawings if no larger than standard page; poor freehand lettering is not acceptable. Prints should not be mounted, stapled, or clipped. They should be labeled on back (lightly in pencil) with name(s) of author(s) and figure number, and the top indicated. Legends should be typed consecutively on a separate sheet. In photographs, identities of patients should be masked. In case of prior publication the author must obtain permission from the previous author and copyright holder to reproduce the figure in the ANNALS. Six illustrations are allowed without cost; above this number the actual cost is charged to the author.

ABSTRACTS: Each paper must be accompanied by an abstract typed in double space and in triplicate (for translation into Interlingua, for *Biological Abstracts*, and for the abstracting service of the J. A. M. A.). Title and authors should be given followed by a concise statement in not more than 250 words of (1) what was done, (2) what was found, and (3) what was concluded.

ABBREVIATIONS

intramuscular	im	centigrade	C	millimeter	mm	volume	vol
intraperitoneal	ip	Fahrenheit	F	centimeter	cm	milliliter	ml
intravenous	iv	specific gravity	sp gr	meter	m	liter	liter
subcutaneous	sc	hemoglobin	Hb	cubic millimeter	mm^3	concentration	concn
by mouth	po	pressure of CO_2	P_{CO_2}	square meter	m^2	microequivalent	μEq
min. lethal dose	MLD	number	no.	weight	wt	milliequivalent	mEq
unit	U	standard deviation	SD	microgram	μg	millimolar	mM
international unit	IU	standard error	SE	milligram	mg	milliosmole	mOsm
minute	min	probability	*P*	gram	g	milligram per cent	mg per 100 ml
calorie (small)	cal	correlation coefficient	R	kilogram	kg		

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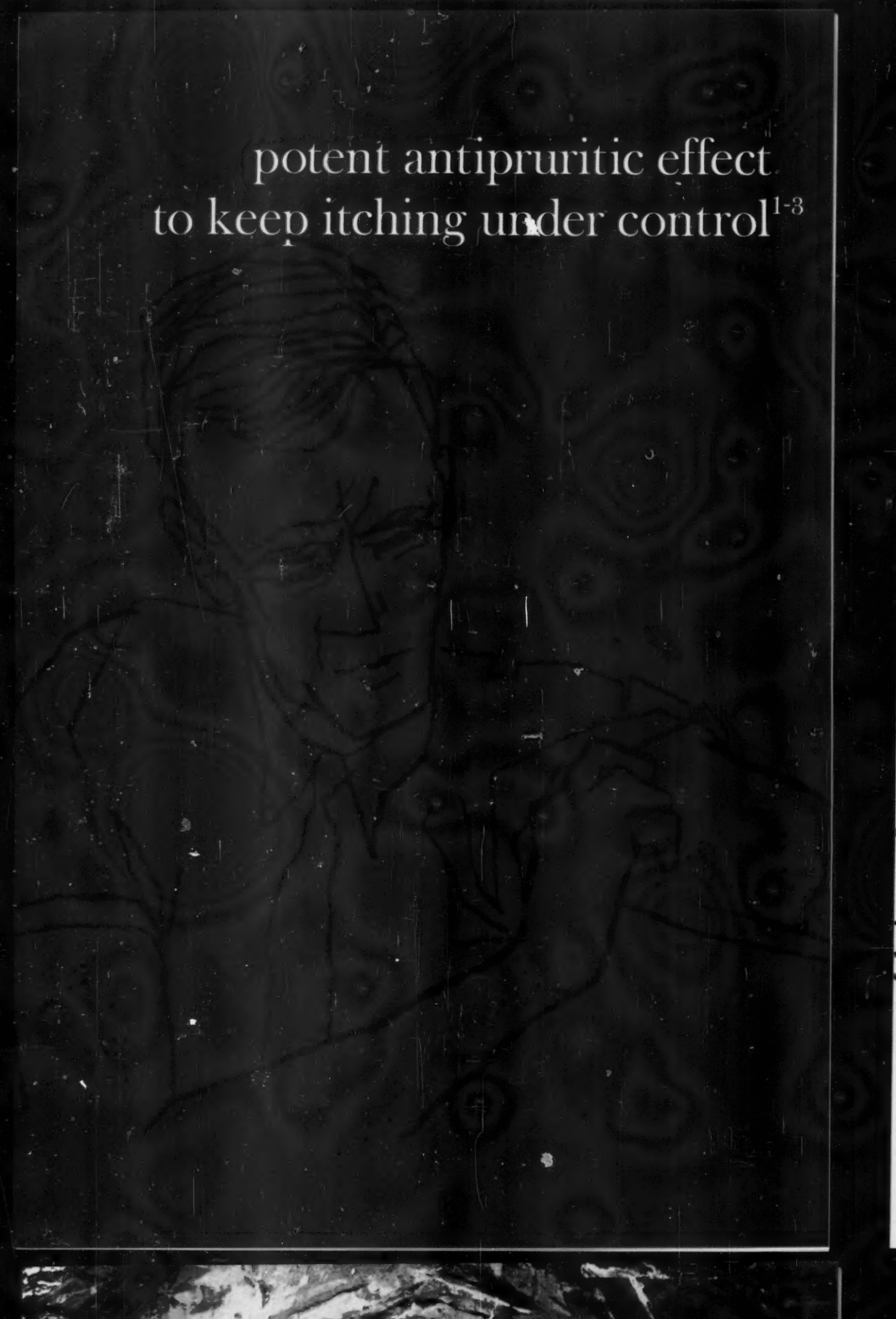
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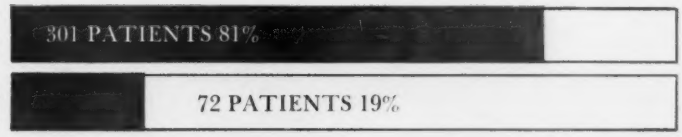

*Adapted from Howell, C. M., Jr.[2]

dosage: *Adults:* Tablets—One tablet (8 mg.) twice daily. Syrup—Two 5 cc. teaspoonfuls (8 mg.) twice daily. Chewable Tablets—Two tablets (7.2 mg.) twice daily. *Children:* One-half adult dosage. Adjustment of dose or interval may be desirable for some patients. **side effects:** Drowsiness has been observed in a small percentage of cases. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently. **contraindications:** There are no known contraindications. **cautions:** If drowsiness occurs after administration of Tacaryl Hydrochloride or Tacaryl Chewable Tablets, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Hydrochloride or Tacaryl Chewable Tablets may display potentiating properties, they should be used with caution in patients receiving alcohol, analgesics, or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice, and orthostatic hypotension, the physician should be alert to their possible occurrence—though no such reactions have been observed with Tacaryl Hydrochloride or Tacaryl Chewable Tablets. **supplied:** Scored tablets, medium coral, 8 mg., bottles of 100. Syrup, 4 mg. per 5 cc. teaspoonful, 16 oz. bottles. Chewable Tablets, pink, 3.6 mg., bottles of 100.

references: (1) Friend, D. G.: Clin. Pharmacol. & Therap. *2*:605-609 (Sept.-Oct.) 1961. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Frohman, I. P.: Methdilazine Hydrochloride in Pruritic Dermatosis, a Doubleblind Evaluation in General Office Practice: M. Times *89* (Dec.) 1961, in press.

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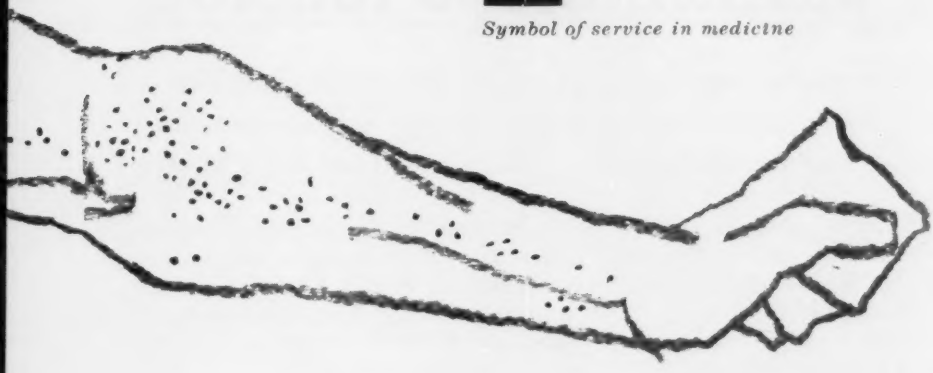

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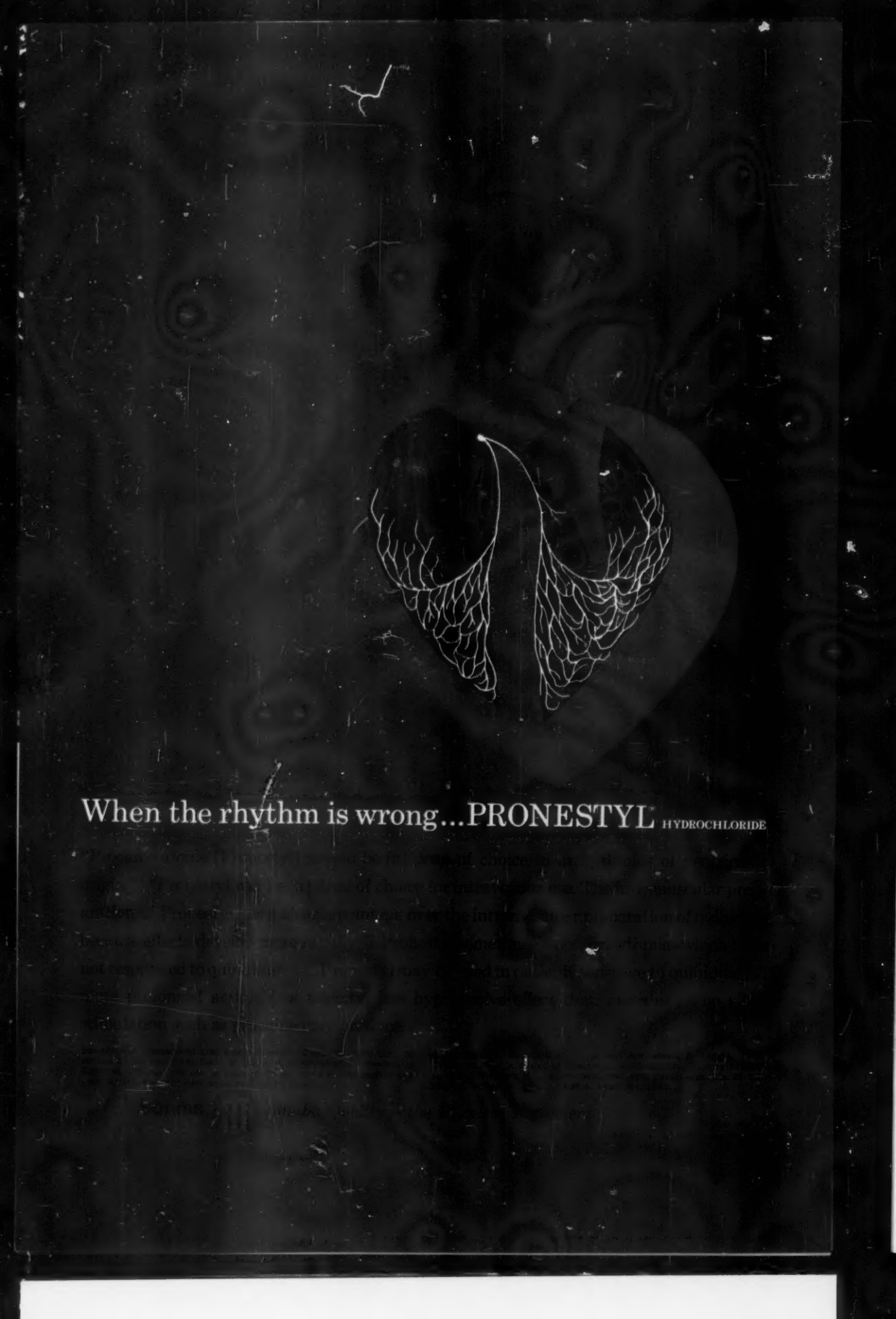
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Indications: **Geriatric debilitation, chronic underweight, pre- and postoperative conditions, convalescence from infection, osteoporosis, gastrointestinal disease, general catabolic conditions, and malnutrition.**

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Precautions: **Use with caution in patients with heart disease or known hepatic damage. Do not continue administration to children beyond 30 days. If masculinizing symptoms develop, discontinue the drug.**

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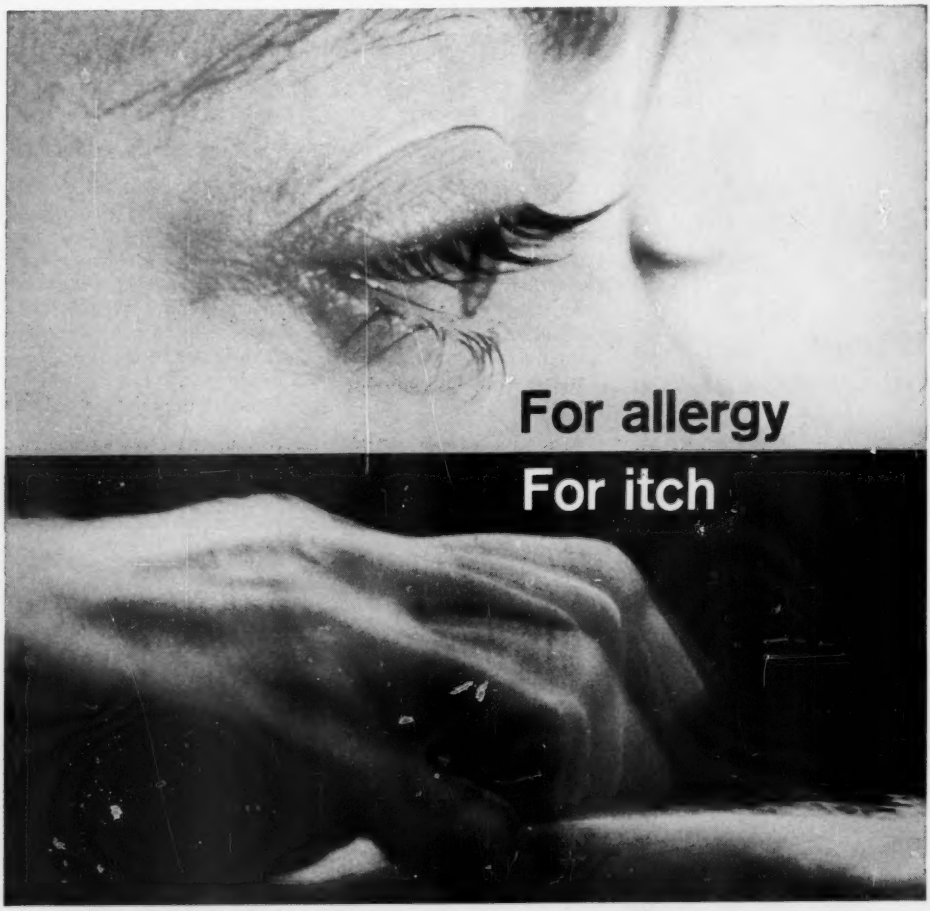

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Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

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references: 1. Kruse, C.A.: Northwest Med. *60*:597 (June) 1961. 2. Chesney, M.A., and Tullis, I.F.: Scientific Exhibit, Annual Meeting, American Medical Assoc., New York City, June 25-30, 1961. 3. Shaw, D.L., Jr.; Chesney, M.A.; Tullis, I.F., and Agersborg, H.P.K., Jr.: Paper read at Sixty-second Annual Meeting, American Therapeutic Society, New York City, June 22-25, 1961.

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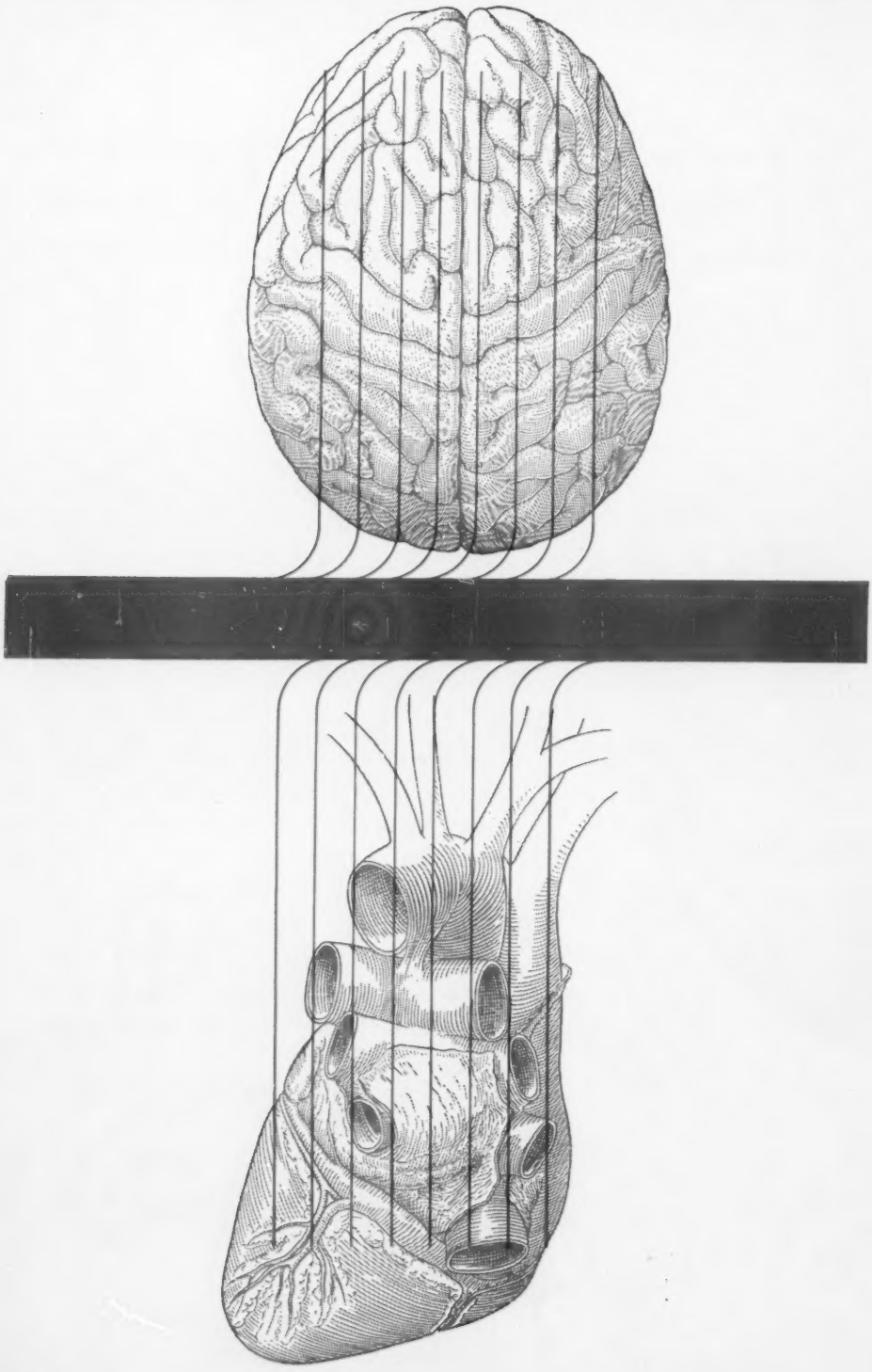

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Selected bibliography from 38 published papers: **1.** W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. **2.** R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. **3.** N. Bloom, *Virginia M. Month.*, *87*:23, 1960. **4.** G. C. Griffith, *Clin. Med.*, *6*:1555, 1959. **5.** G. C. Griffith, *Dis. Nerv. System*, *21*:(Suppl.), 101, 1960. **6.** L. Alexander and S. R. Lipsett, *Dis. Nerv. System*, *20*:(Suppl.), 26, 1959.

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1. Mintz, A. A.: Antibiot. Med. 7:481, 1960.

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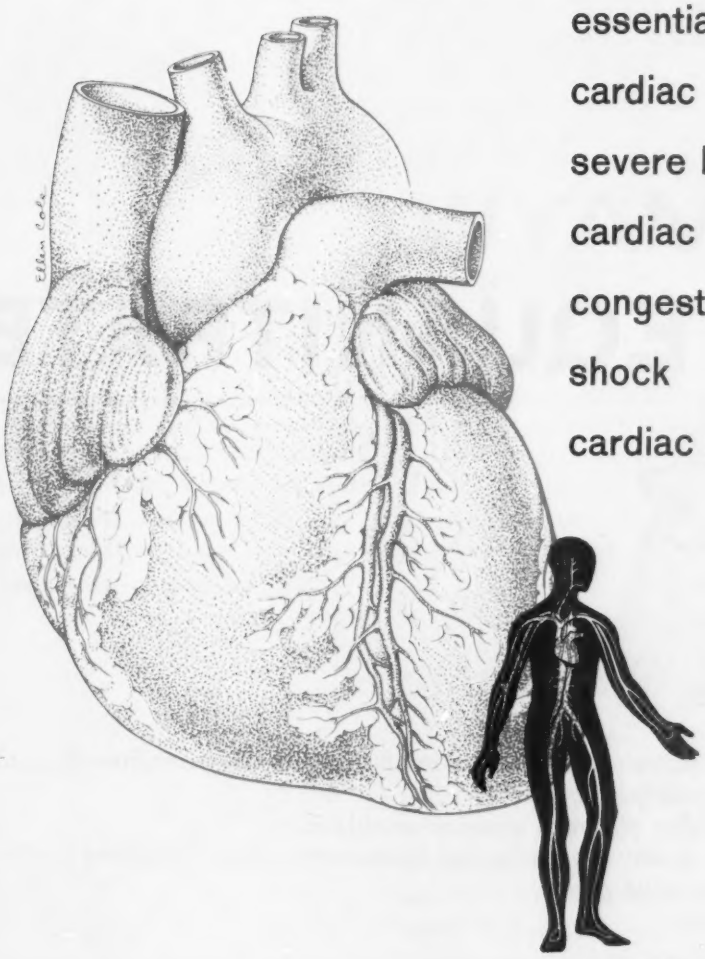

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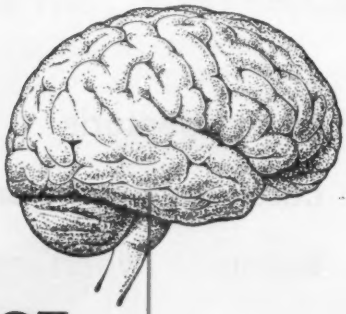

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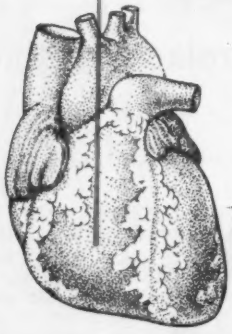

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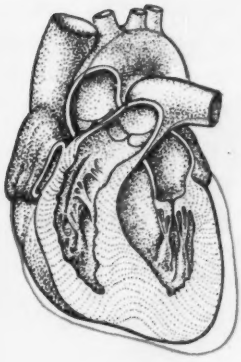
in SHOCK

and cardiac arrhythmias



WYAMINE helps reverse the physiological response to the shock state. It increases blood flow to vital organs by stimulating myocardial contraction with minimal peripheral constriction.[1] It has a unique antiarrhythmic effect; is valuable in shock of myocardial infarction,[2] hypotension of severe illness,[3] cardiac arrhythmias,[4] hypotension attending anesthesia.[5]

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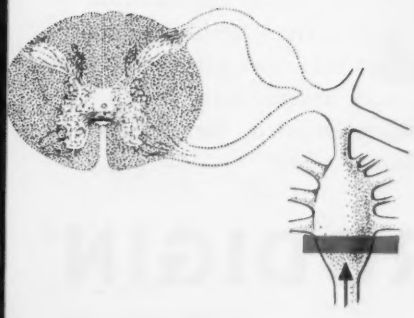
in DIASTOLIC hypertension



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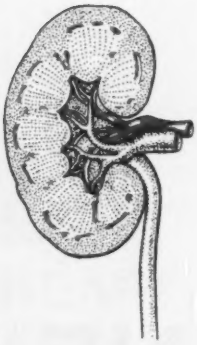
in cardiac edema



Parenteral THIOMERIN produces rapid, predictable, and smooth fluid loss in severe edematous states[1-3] such as cardiac edema (peripheral or pulmonary), nephrotic edema, ascites of liver disease. Virtual freedom from local irritant actions commends use of THIOMERIN subcutaneously[4] as well as I.M. or I.V. Systemic and cardiac toxicity are extremely low.

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References: 1. Modell, W. in Modell, W.: Drugs of Choice, 1958-1959, The C. V. Mosby Co., St. Louis, 1958, p. 87. 2. Burch, G.E.: J.A.M.A. 157:1073 (March 26) 1955. 3. Brimi, R.J.: Journal-Lancet 70:298 (Aug.) 1950. 4. A.M.A. Council on Drugs: New and Nonofficial Drugs, J. B. Lippincott Co., Phila., 1959, p. 599. 5. Friedman, M.: Modern Concepts of Cardiovascular Disease (The American Heart Assoc.) 25:311 (Feb.) 1956. 6. Gold, H., et al.: J. Pharm. & Exper. Therap. 109:45 (Sept.) 1953.

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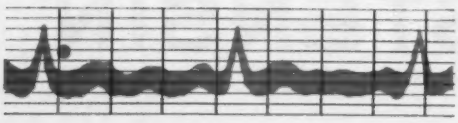

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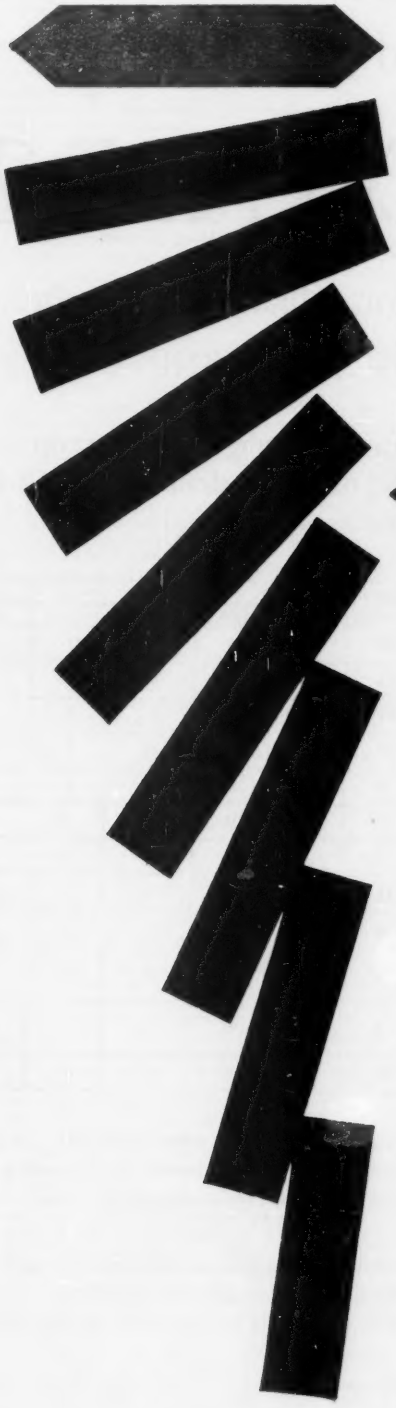

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CYTOTOXIC AGENT for palliative chemotherapy of certain types of malignant neoplasms

Cytoxan demonstrated therapeutic advantage over certain other agents in a recent 12-month study* of 130 patients, most of whom were refractory to previous treatment:

DISEASE	NUMBER OF PATIENTS	RESULTS				INADEQUATE TRIAL
		GOOD	FAIR	TRANSIENT	FAILURE	
Lymphoma	74	34	3	5	23	9
Hodgkin's Disease	29	10	3	4	9	3
Lymphosarcoma	21	15	0	0	3	3
Multiple Myeloma	16	9	0	0	4	3
Reticulum Cell Disease	8	0	0	1	7	0
Leukemia	23	10	0	0	8	5
Chronic Lymphatic Leukemia	8	4	0	0	3	1
Acute Monoblastic Leukemia	11	5	0	0	3	3
Acute Myeloblastic Leukemia	4	1	0	0	2	1
Carcinoma (Breast, Lung, and Solid Tumors)	29	2	1	1	23	2
Miscellaneous (Mycosis Fungoides, Psoriasis)	4	0	0	1	3	0
Total	130	46	4	7	57	16

Adapted from Wall, R. L., and Conrad, F. G.*

Note that the neoplastic disorders most responsive to Cytoxan were lymphosarcoma, multiple myeloma, Hodgkin's disease, and chronic lymphatic leukemia. Occasionally, good results were observed in acute monocytic leukemia and carcinoma of the breast.

Other advantages noted in this study*

• multiple routes of administration, permitting prolonged maintenance therapy • lack of latency period for bone marrow depression • failure to produce significant thrombocytopenia • potential therapeutic effect in diseases usually unresponsive to other mustard compounds (*e.g.*, myeloma).

*Wall, R. L., and Conrad, F. G.: Arch. Int. Med. *108*:456-482, 1961.

INDICATIONS: Cytoxan is valuable for palliative therapy of certain malignant neoplasms, particularly some of those arising in the reticuloendothelial and hematopoietic systems and certain solid tumors.

Types of cancer which have proved relatively more susceptible or more resistant to Cytoxan therapy may be grouped as follows:

Group I: Neoplasms relatively susceptible to Cytoxan
- Hodgkin's disease
- Lymphomas: lymphosarcoma; giant follicular lymphoma; reticulum cell sarcoma
- Leukemia: acute; chronic
- Mycosis fungoides

Group II: Neoplasms relatively resistant to Cytoxan
- Malignant neoplasms of the breast and the ovary*
- Malignant neoplasms of the lung, the gastrointestinal tract and the genitourinary system, including the cervix and the uterus
- Malignant neoplasms of miscellaneous origin
- Malignant melanomas

*Malignant tumors of these organs are somewhat more susceptible to Cytoxan therapy than are the others included in this group.

DOSAGE: *For neoplasms relatively susceptible to Cytoxan* – Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2 to 3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan – Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage – The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient. Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

ADMINISTRATION: Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

PRECAUTIONS: Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2 to 3 weeks, or debilitated patients.

AVAILABILITY: Cytoxan is available as follows:

Cytoxan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.

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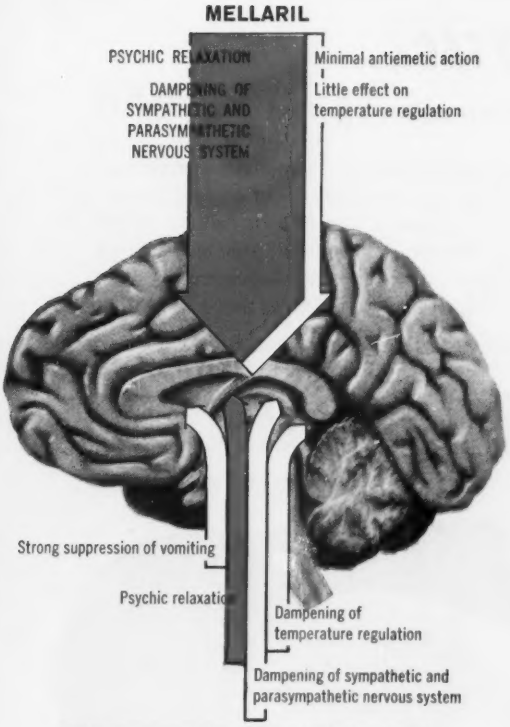

"The side-effects which we have observed during trials with Mellaril have not been of a serious nature and we believe that the claim can justly be made that Mellaril has fewer side-effects than any other of the phenothiazine compounds."[2]

greater specificity of tranquilizing action results in fewer side effects

1. Mellaril has a specificity of tranquilizing action on certain brain sites, in contrast to the more "diffuse" action of other phenothiazines. For example, unlike other phenothiazine tranquilizers, Mellaril provides tranquilization without any significant antiemetic action.
2. Mellaril has less "spill-over" action to other brain areas. Hence, such extrapyramidal effects as parkinsonism are rare.
3. Jaundice has not been observed.

Mellaril is indicated for agitation, apprehension and anxiety, ranging from mild to severe, in both ambulatory and hospitalized patients.

ADULT DOSAGE – Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d. Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily.

CHILDREN'S DOSAGE – Average 10 mg. t.i.d. (range: 20 – 40 mg. per day).

Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg., 200 mg.

PRECAUTIONS: Leukopenia and/or agranulocytosis, photosensitization and convulsive seizures have been reported with long-range therapy but are very rare. Jaundice has not been observed during the use of Mellaril. Pseudoparkinsonism and other extrapyramidal disorders may occur but are infrequent and mild. Pigmentary retinopathy, which has been observed in psychiatric patients taking large doses (in excess of 1600 mg. daily over long periods of time) is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication is avoided by remaining within the recommended limits of dosage. Drowsiness is not infrequent, especially with large doses and during early treatment. Dryness of the mouth, nasal stuffiness, skin eruption, nocturnal confusion, galactorrhea and amenorrhea are noted occasionally. Some male patients have complained of inability to ejaculate. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

1. Judah, L., Murphree, O., and Seager, L.: Am. J. Psychiat. 115:1118, June 1959.
2. Sandison, R. A., Whitelaw, E., and Currie, J. D. C.: Clinical trials with Mellaril in the treatment of schizophrenia, Journal of Mental Science (British Journal of Psychiatry) 106:732, April 1960.

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ORIGINAL RESEARCH SERVING THE PHYSICIAN

LESS CHANCE OF ATTACK...

with hundreds of pellets of protection against ANGINA

A 30 mg. Pentritol Tempule containing hundreds of pellets for 12 hour action produces a smooth, prolonged response. Duration, frequency, and severity of anginal attacks are lessened.[1] Angina patients showing little progress with 80 mg. daily of PETN tablets, have responded favorably to the smaller dose of Pentritol Tempules.[2] Kamil and Klinger report excellent results from a timed-disintegration pentaerythritol tetranitrate capsule, with nitroglycerin requirements reduced as much as 85%.[3]

1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. 59:3398, 1959.

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controlled disintegration capsules

Pentritol Tempule magnified approximately 9 times.

actual size

PENTRITOL—Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown excellent results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity of physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol-B Tempules, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

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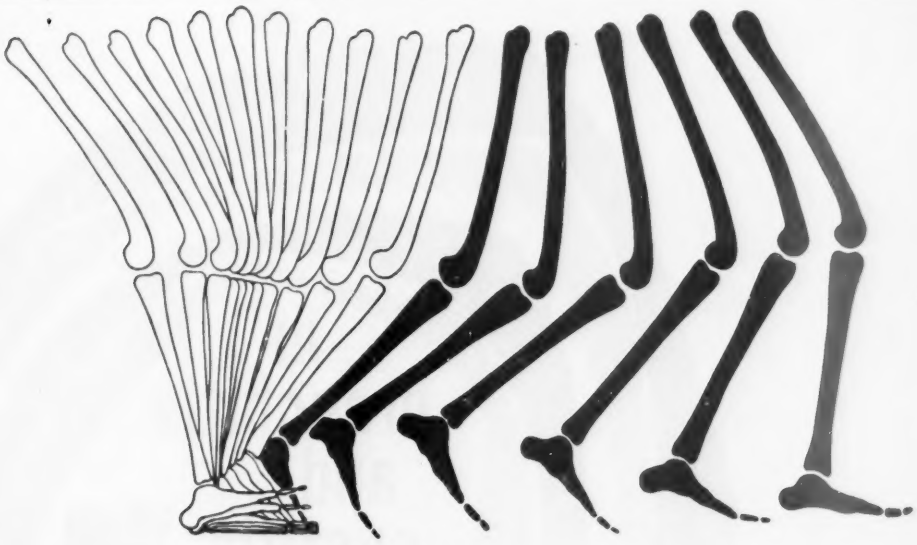

Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.[1] "Post-injection flare-up was practically non-existent."[1]

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off.
methylprednisolone acetate, Upjohn

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relief within hours... lasting for weeks

Depo-Medrol* intra-articularly

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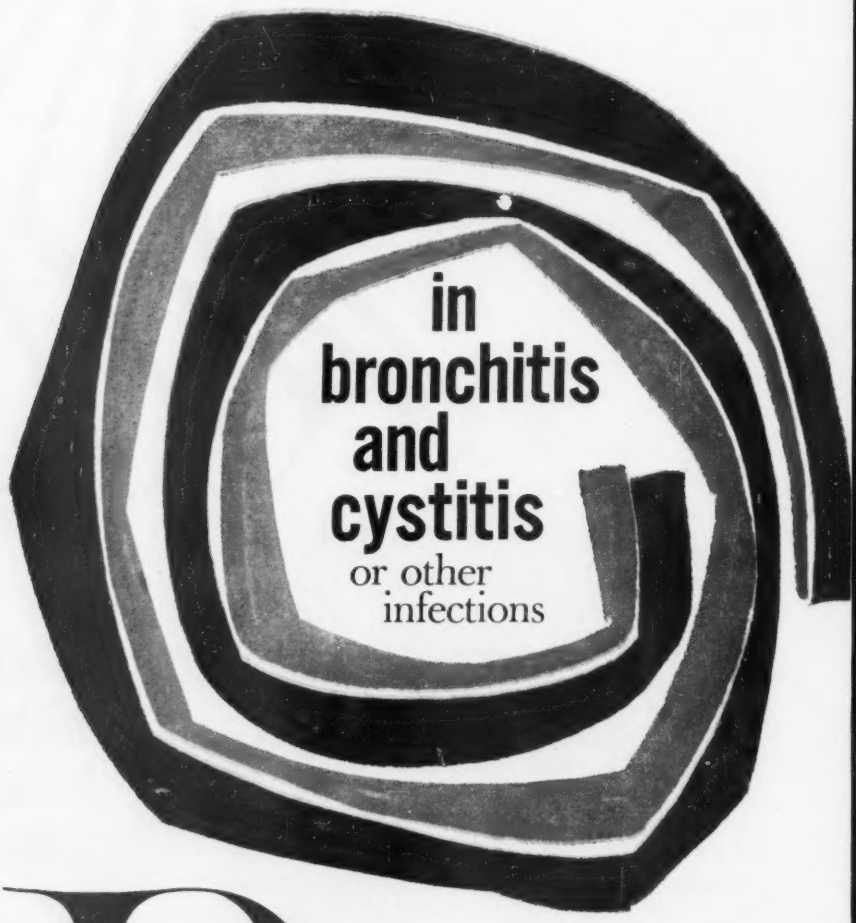

antibiotic therapy with an

DECLO

CAPSULES, 150 mg., 75 mg. *Dosage:* Average infections—150 mg. four times daily. Severe infections—Initial dose of 300 mg., then 150 mg. every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. *Dosage:* 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into four doses.

SYRUP, 75 mg./5 cc. teaspoonful (cherry-flavored). *Dosage:* 3 to 6 mg. per pound body weight per day—divided into four doses.

PRECAUTIONS — As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication.

Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics, and demands that the patient be kept under constant observation.

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against relapse—up to 6 days' activity on 4 days' dosage

against secondary infection—sustained high activity levels

against "problem" pathogens—positive broad-spectrum antibiosis

Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1-6]; gout,[1,7,8]; acute superficial thrombophlebitis[9,10]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1,7]; severe forms of a variety of local inflammatory conditions.[11,12,13]

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing.

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far more potent than salicylates—Anti-inflammatory potency of Tandearil markedly superior to aspirin.[2,15]

availability:
Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

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references:
1. Graham, W.: Canad. M. A. J. **82**:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Kiem, I. M.: Arth. and Rheumat. **2**:212, 1959. 3. O'Reilly, T. J.: J. Irish M. A. **46**:106, 1960. 4. Cardoe, N.: Ann. Rheumat. Dis. **18**:244, 1959. 5. Robichaux, E.: General Practice **24**:14, 1961. 6. Brooke, J. W.: Western Med. **2**:81, 1961. 7. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. **98**:31, 1959. 8. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 9. Stein, I. D.: Ann. N. Y. Acad. Sc. **86**:307 (March 30) 1960. 10. Barczyk, W., and Röth, W.: Praxis **49**:589, 1960. 11. Miller, J. M., et al.: Antibiotic Med. and Clin. Therap. **7**:109, 1960. 12. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. **97**:429, 1959. 13. Summary of individual case histories submitted to Geigy. 14. Domenjoz, R.: Ann. N. Y. Acad. Sc. **86**:263, 1960. 15. Smyth, C. J.: Ann. N. Y. Acad. Sc. **86**:292, 1960. 16. Yü, T. F., et al.: J. Pharmacol. and Exper. Therap. **123**:63, 1958.

1081-61

when your patient's excessive gas is TRAPPED GAS

"... the distress is due not so much to spasm of the muscle as to excessive formation of gas in the bowel, or failure of the bowel to absorb or pass it on quickly and comfortably."[1]

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DOSAGE:

Two tablets t. i. d. Three tablets t. i. d. in severe cases.

SUPPLIED:

Bottles of 100 and 500.

1. Alvarez, W. C., "Modern Medicine Annual" 1957, page 11.

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STEROIDS: FAR FROM ROUTINE THERAPY IN RHEUMATOID ARTHRITIS. "... it would now appear that the steroids should be employed infrequently in rheumatoid arthritis, and, when used, long-continued therapy should be avoided and the dosage reduced to the lowest possible level." [New and Nonofficial Drugs 1961, Philadelphia, J. B. Lippincott Co., 1961, p. 598.]

PLAQUENIL: EFFECTIVE LONG-TERM THERAPY THAT SPARES STEROIDS. Many physicians are now evaluating Plaquenil, the non-steroid antirheumatic of choice. Quite simply, Plaquenil provides conservative, safer, long-range management of rheumatoid arthritis. While the steroids often result in dramatic short-term improvement, Plaquenil affords a more practical, lasting solution to the long-term problems of this long-term disease, and makes it possible to utilize steroids sparingly.

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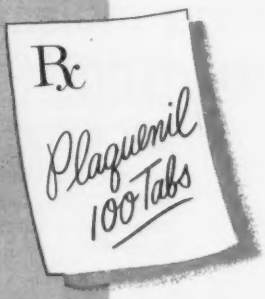
... provides conservative therapy
... affords lasting benefits
... spares steroids
... is generally well tolerated

PLAQUENIL ... acts cumulatively
... reduces need for steroids
... reduces need for analgesics
... works in conjunction with both steroids and aspirin

PLAQUENIL ... produces major improvement in 60 to 83 per cent of patients
... results in a low incidence of major relapse



Before prescribing, be sure to consult Winthrop's literature for additional information about dosage, possible side effects and contraindications.

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NON-STEROID ANTIRHEUMATIC FOR SAFE, LONG-TERM THERAPY

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For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

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BRAND OF CHLORPROPAMIDE

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with oral therapy

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at presently recommended dosage has a low incidence of adverse effects which require discontinuance of therapy. See "In Brief."

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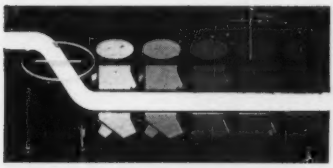

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ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

As with insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function.

DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

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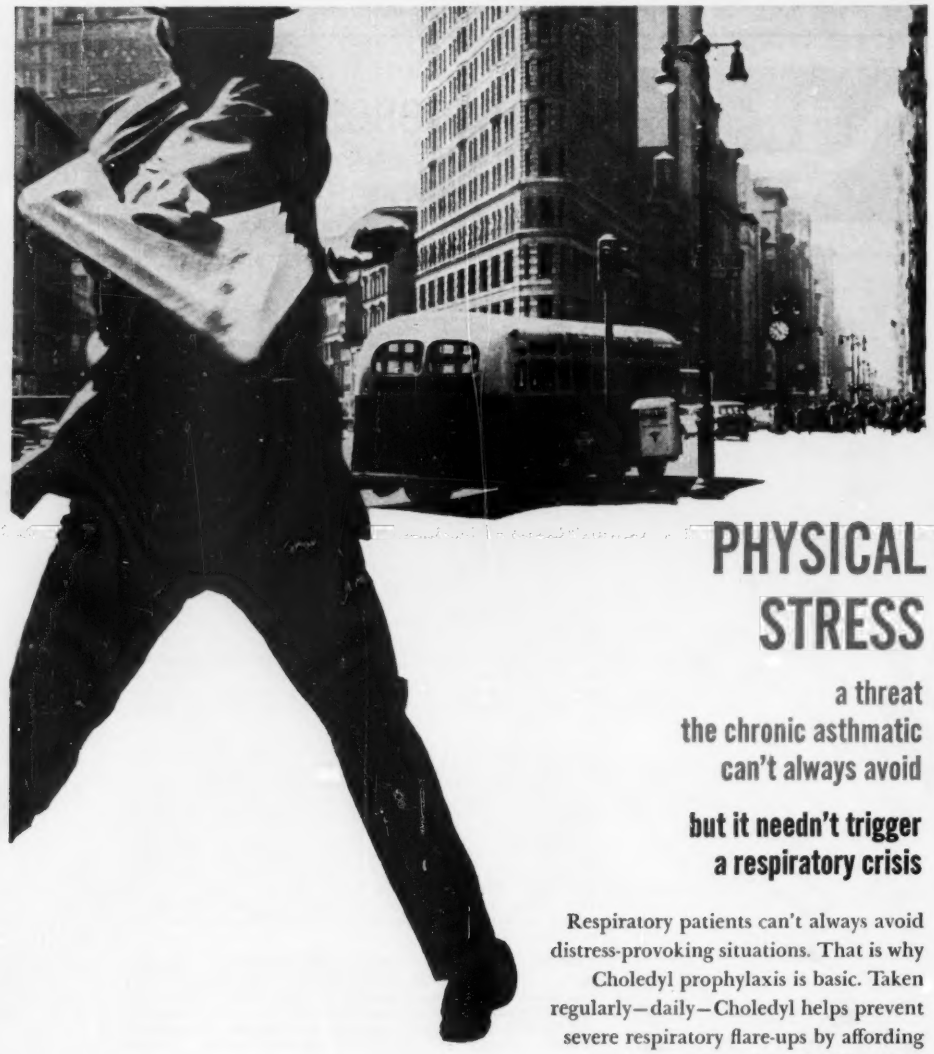

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but it needn't trigger a respiratory crisis

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to avoid the crisis in chronic bronchitis, chronic asthma, emphysema

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a superior antihistamine with minimal side effects
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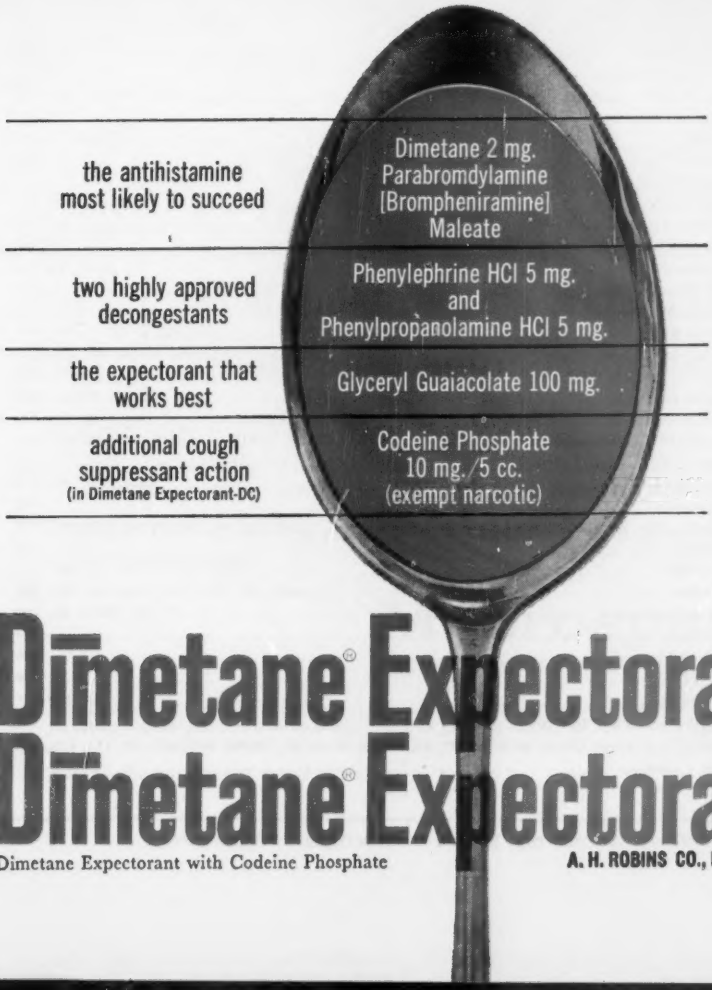
an effective, safe expectorant to increase respiratory tract fluid
a reliable cough suppressant for those patients who need added potency

what most coughers need

now in a single teaspoon (5 cc.)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Phenylephrine HCl 5 mg. and Phenylpropanolamine HCl 5 mg.
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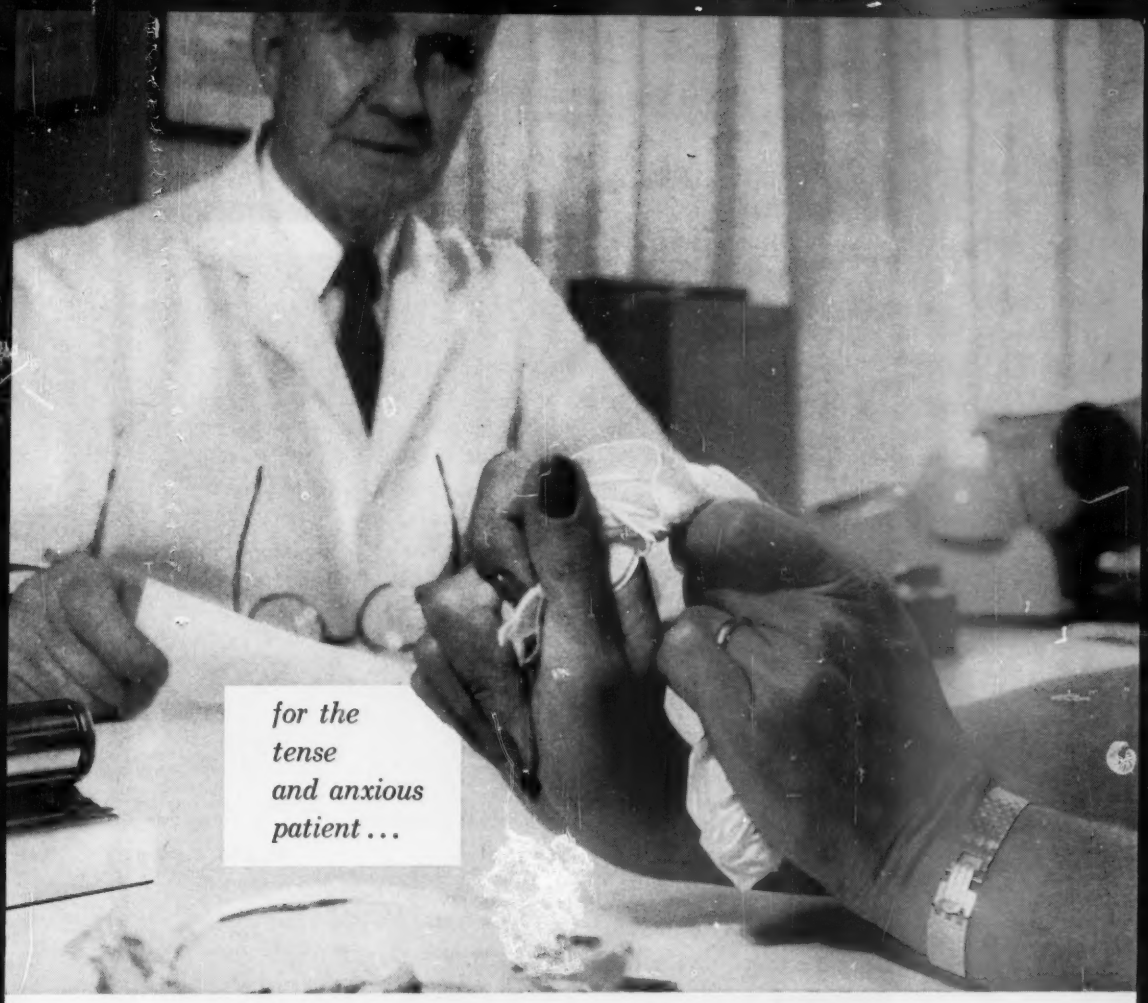


the only sustained-release tranquilizer that does not cause autonomic side reactions

- SAFE, CONTINUOUS RELIEF of anxiety and tension for 12 hours with just one capsule—without causing autonomic side reactions and without impairing mental acuity, motor control or normal behavior.
- ECONOMICAL for the patient—daily cost is only a dime or so more than for barbiturates.

Meprospan®-400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: *Meprospan-400*, each blue-topped capsule contains 400 mg. Miltown (meprobamate). *Meprospan-200*, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.

WALLACE LABORATORIES / *Cranbury, N. J.*

CME-4232

FOR COUGH AND COLD DEMONS...

NON-NARCOTIC

ULO®

for control of acute cough regardless of etiology

ULOMINIC®

for control of acute cough and associated allergic reactions

ULOGESIC®

for control of acute cough and for relief from associated muscular aches, pain and fever

ULO

ULOMINIC

ULOGESIC

INHIBITS COUGH IMPULSE FOR 4 TO 8 HOURS
the threshold of the medullary cough center is elevated while the cough reflex is not abolished.

COUNTERACTS IRRITATION IN PHARYNX, LARYNX, TRACHEA AND BRONCHI
inhibits tendency of histamine to cause edema of the nasopharyngeal mucosa, local irritation, and vasodilation.

RELIEVES CONGESTION
reduces postnasal discharge, lessens irritation to pharyngeal and laryngeal membranes.

MAKES VOLUNTARY COUGH MORE PRODUCTIVE
loosens and liquefies mucus, soothes irritated bronchial mucosa.

Ulogesic enlarges the therapeutic dimensions of Ulominic

ALLEVIATES ASSOCIATED ACHES AND DISCOMFORTS AND ABORTS FEVER
elevates the pain threshold with an analgesic potency the same as acetanilid, with much less toxicity.

ULO®
non-narcotic antitussive molecule chlophedianol HCl

DIAFEN®
fast-acting antihistaminic diphenylpyraline HCl

PHENYLEPHRINE HCl
sympathomimetic

GLYCERYL GUAIACOLATE
expectorant and demulcent

APAP
acetyl-p-aminophenol analgesic and antipyretic

FORMULAS:

ULO SYRUP—Each 5 ml. teaspoonful contains:

chlophedianol • HCl* [alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol • HCl]	25 mg.
chloroform, U.S.P.	0.001 ml.

Alcohol 6.65 per cent in a pleasant flavored syrup base

ULOMINIC® SYRUP — Each teaspoonful (5 cc) contains:

chlophedianol HCl* [alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol • HCl]	15.0 mg.
diphenylpyraline HCl (1-methyl-4-piperidyl-benzhydryl ether • HCl)	1.0 mg.
phenylephrine HCl	5.0 mg.
glyceryl guaiacolate	100.0 mg.
alcohol	6%

ULOGESIC® — Each tablet contains:

chlophedianol HCl* [alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol • HCl]	7.5 mg.
diphenylpyraline HCl (1-methyl-4-piperidyl-benzhydryl ether • HCl)	0.5 mg.
phenylephrine HCl	2.5 mg.
glyceryl guaiacolate	25.0 mg.
acetaminophen	162.5 mg.

*Patents pending

INDICATIONS: For acute cough associated with:

Upper Respiratory Infections
Common Cold
Influenza
Pneumonia
Pertussis
Pleurisy
Bronchitis
Tracheitis
Laryngitis
Croup
Allergies (Ulominic and Ulogesic)

CONTRAINDICATIONS: Although no contraindications for ULOMINIC or ULOGESIC are known, they should be used only for acute cough.

CAUTION: Since ULOMINIC and ULOGESIC contain an antihistaminic agent, drowsiness may occur. As they also contain a sympathomimetic agent, they should be used with caution in coronary artery disease, glaucoma, hypertension, and hyperthyroidism.

SIDE EFFECTS:

ULO
These occur only occasionally and have been mild. Nausea and dizziness have occurred infrequently; vomiting and drowsiness rarely. As with all centrally acting drugs, an infrequent case may develop excitation, hyperirritability and nightmares. The symptoms disappear within a few hours after the drug is discontinued. In three cases (1 adult and 2 children) where the drug was continued in large or even excessive amounts after stimulation was present, hallucinations developed. Upon withdrawal of the medication, the patients recovered rapidly within a few hours.

ULOMINIC and ULOGESIC
Side effects from ULOMINIC or ULOGESIC occur occasionally and are mild. Nausea, dizziness, and dryness of the mouth occur infrequently; vomiting and drowsiness rarely.

DOSAGE:

ULO
Adults: 25 mg. (1 teaspoonful) 3 or 4 times daily as required.
Children: 6 to 12 years of age—12.5 to 25 mg. (½ to 1 teaspoonful) 3 or 4 times daily as required;
2 to 6 years of age—12.5 mg. (½ teaspoonful) 3 or 4 times daily as required.

ULOMINIC
Adults: One teaspoonful (5 cc) four times daily.
Children: 6 to 12 years—½ teaspoonful (2.5 cc) 4 times daily.
2 to 6 years—¼ teaspoonful (25 drops) 4 times daily.

ULOGESIC
Adults: Two tablets 4 times daily.
Children: 6 to 12 years—one tablet 4 times daily.

AVAILABILITY:

ULO SYRUP
Bottles 12 oz.

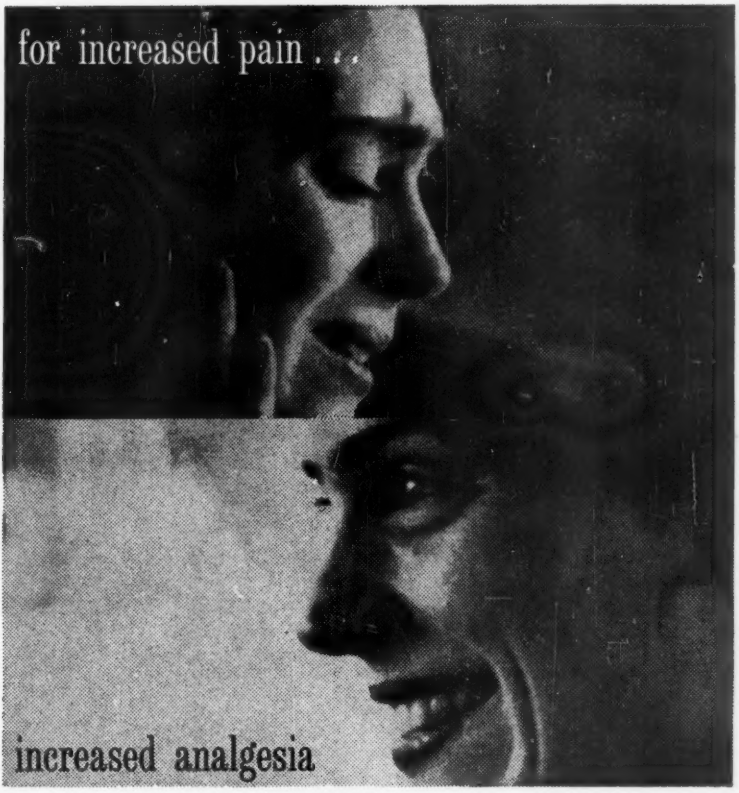
ULOMINIC SYRUP
Bottles 1 pint

ULOGESIC TABLETS
Bottles of 100 tablets.

CAUTION: Federal Law prohibits dispensing without prescription.

Riker

RIKER LABORATORIES, INC., Northridge, California



DARVON® COMPOUND-65

Darvon Compound-65 provides twice as much Darvon® as does regular Darvon Compound without increase in salicylate content or size of the Pulvule®. Usual dosage is 1 Pulvule three or four times daily.

Darvon Compound		Darvon Compound-65
32 mg.	Darvon	65 mg.
162 mg.	Acetophenetidin	162 mg.
227 mg.	A.S.A.®	227 mg.
32.4 mg.	Caffeine	32.4 mg.

Product brochure available; write Eli Lilly and Compar:, Indianapolis 6, Indiana.

Darvon® Compound (dextro propoxyphene and acetylsalicylic acid compound, Lilly)
Darvon® (dextro propoxyphene hydrochloride, Lilly)
A.S.A.® (acetylsalicylic acid, Lilly)

Lilly

120351

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